Exhibit B

Expert Opinion Report

Gilbert W. Moeckel M.D., Ph.D., FASN

In Re: Proton Pump Inhibitor Products Liability Litigation (No. II) (MDL 2879)

Prepared for:

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BACKGROUND, EDUCATION, AND QUALIFICATIONS OF EXPERT

I am a physician licensed to practice in the State of Connecticut since 2008. I have been board certified by the American Board of Pathology in 2008 and 2018.

I am currently Professor of Pathology, Director of the Renal, Cardiac & Transplant Pathology & Electron Microscopy Laboratory and Director of the Renal & Genitourinary Pathology Fellowship Program at Yale University School of Medicine in New Haven, Connecticut.

For over 30 years, I have dedicated my medical practice to curing kidney diseases. My research is focused on better understanding the progression of chronic kidney disease. With regard to my qualifications to serve as an expert in this litigation, I provide the following information.

I received my medical degree in 1989 from the Ludwig Maximilian Universität in Munich, Germany. In 1993, after completing my Ph.D. with Magna Cum Laude I moved to the Department of Medicine at the University of Arizona HSC in Tucson, Arizona to begin post-doctoral fellowship training. In 1996, I completed a 3-year postdoctoral research fellowship in Nephology. Thereafter, I completed a three-year residency program in the Department of Pathology, and, upon completion, I was named Pathology Chief Resident. While serving as Chief Resident, I also completed sub-specialized training in Renal Pathology and Surgical Pathology.

In 2000, I joined the faculty at the Vanderbilt University Medical Center in Nashville, Tennessee where I served for nearly 8 years as Assistant Professor in Pathology. During this time, I also served as Visiting Research Professor in the Department of Pathology at the University of Arizona HSC.

I have extensive experience as an investigator in experimental pathology and in research of pathological mechanisms of kidney diseases. My research has been sponsored by the

Department of Defense (DOD), the National Institute for Digestive and Diabetic Kidney Diseases (NIDDK) at the National Institutes of Health (NIH), as well as by pharmaceutical companies (Boehringer Inc.) and academic institutions.

I presently serve, and have served in the past, as a peer reviewer for the National Science Foundation and the American Heart Association. I also serve and have served as Editorial Board Member for several journals in physiology and nephrology. I am currently responsible for the review of manuscripts for the Journal of American Society of Nephrology, Nephrology Dialysis & Transplantation, Kidney International and International Scholarly Research Network (ISRN).

For nearly 20 years, I have been invited to lecture at annual meetings for medical societies including at the international Kidney Week meeting sponsored by the American Society of Nephrology (ASN).

From 2005 - 2009, I served as Advisory Committee Member on OSPS-Induced Renal Injury, an organization established by FLEET Inc. and concerned with phosphate-induced acute kidney injury.

I have been recognized by international and national professional societies. For example, I received the Travel Award, to attend "Concepts in Molecular Biology" by the American Society for Investigative Pathology in 1998. The Academy of Clinical Laboratory Physicians and Scientists honored me with the Paul E. Strandjord Young Investigator Award. I was named a Fellow of the American Society of Nephrology. The Endourological Society World Congress designated my research as 2nd place at the 2004 Annual Essay Contest. Since 2011, I have been designated an Invited Member, Nephropathology Working Group, European Society of Pathology. In 2000, I was honored to receive Outstanding Resident Teaching in Pathology Award granted by the University of Arizona College of Medicine. During my tenure at Vanderbilt, I received the

Vanderbilt Physician Scientist Development Award. In 2015, at Yale, I received the Department of Pathology's Averill A. Liebow Award for Excellence in Teaching Pathology Residents.

I have authored more than 100 peer-reviewed original reports and publications, as well as editorials, reviews and book chapters on topics related to chronic kidney disease and other renal injuries. I have also authored a case report of particular relevance to this expert report (see Ni N, Moeckel GW, Kumar C. *Late-onset omeprazole-associated acute interstitial nephritis*. J Am Geriatr Soc. 2010 Dec; 58(12):2443-4).

I am a past and present member of several editorial boards that publish peer-reviewed scientific literature. Presently, I am a reviewer for the following journals: Journal of Cell Physiology; Journal of American Society of Nephrology; Nephrology Dialysis & Transplantation; American Journal of Physiology; Annals of Internal Medicine; and Kidney International.

A copy of my *curriculum vitae* concerning further detail as to my background, education, training and publications are attached.

SUMMARY OF OPINIONS

1. Takeda animal studies showed nephrotoxic signals of renal tubular (and other) renal injuries of greater severity with increasing dose and duration in test animals compared with controls.

2. Takeda failed to fully assess the nephrotoxic potential of PPIs in the nonclinical setting despite the aforesaid findings.

3. There are biologically plausible mechanisms by which PPIs induce tubular injury in the kidneys of test animals that are relevant in humans.

4. By failing to investigate the tubular renal signals seen in PPI-dosed animals, Takeda allowed a drug with subclinical, nephrotoxic potential to enter the market for popular use in humans.

EXPERT APPROACH AND METHODOLOGICAL ASSESSMENT

Similar to my approach regarding the non-clinical studies sponsored by AstraZeneca and Pfizer Wyeth,[1] I first sought to obtain information about the nonclinical testing programs performed by Takeda and/or its predecessor entities and/or other entities that initially held the New Drug Application for Lansoprazole and Dexlansoprazole).[2] In approaching this task, I considered and relied on defendant-manufacturer regulatory submissions, consisting of, among other things, non-clinical trial indices and study reports. I also considered documents produced as part of the litigation process, deposition testimony, and other company-specific documents.[3]

As in the case of my approach to the AstraZeneca and Pfizer Wyeth non-clinical studies, after determining the extent and type of studies performed for each of these products, I determined those studies that would provide the most useful and relevant information for me to form my opinions. My choice of studies to review for each of the PPI products is based upon my experience and training as a renal pathologist and kidney disease researcher. These studies included, among others, the nonclinical studies submitted to support the clinical use of PPIs, as identified in regulatory submissions, where the kidneys of test animals had been harvested and examined. I relied on the list of non-clinical studies produced at the non-clinical Takeda 30(b)(6) deposition (Crawford-4). I asked to see kidney tissue from studies of different types and treatment periods to detect whether lesions suggestive of drug toxicity manifested as acute insults and/or chronic lesions. I analyzed studies performed on both young and old animals of different species to discern whether renal effects were consistent (or not) across different age groups and different species. I also examined studies that utilized different routes of administration (e.g., oral gavage vs. intravenous) and different dosing regimens, both high dose studies as well as those in which the

[1] See "Proton Pump Inhibitor Toxicity Expert Witness Report" by Gilbert W. Moeckel, M.D., Ph.D. dated April 22, 2021.

[2] Testing of the PPI products was also conducted by predecessor companies of the manufacturer-defendants (including TAP and Abbot) and/or by contract research organizations (CROs) retained by the companies.

[3] In addition to indices and studies themselves, I reviewed the document entitled: "Notes on lansoprazole and dexlansoprazole nonclinical toxicity studies" authored by Dr. Stuart Levin, Ph.D. dated February 5, 2019, ("Levin Notes" or "Levin Report") with appendix entitled "February 6, 2019 PPI MDL- Preclinical Studies Provided to Dr. Stuart Levin."

doses administered to test animals more closely approximated therapeutic doses in marketed PPI products for use in humans.

I reviewed the reports described above and identified lesions in the kidney that occurred in greater numbers and in greater degrees of severity in the dosed animals versus the controls. I noted that the reviewing pathologists typically diagnosed these lesions as species-specific, age-related changes that are irrelevant in humans, with, at times, only limited descriptions of the tissues examined. Therefore, I asked to examine the harvested renal tissues, to the extent available, in the form of slides or otherwise (preserved renal/ kidney tissue; renal/kidney histopathology slides microscopic photographs or other contemporaneous color imaging) to determine possible etiologies for the pathologic descriptions contained within the study reports I reviewed for each of the aforesaid products.

TAKEDA NONCLINICAL STUDIES

I received 3 external hard drives containing over 7,000 digitalized images of kidney tissue sections from a variety of experimental animals from twenty preclinical studies.[4] Using a digital slide reader software, I reviewed each image, noted the pathological findings and created screenshots of the histopathological lesions appearing in the images. Below is a discussion of the studies for which I received pathology slides that I consider to be most relevant to my opinion that PPIs cause tubular injury. A brief discussion of other non-clinical studies for which I received pathology images can be found by individual study number in Appendix A attached to this report. In Appendix B (also attached to this report), I discuss other non-clinical studies by individual study

[4] Studies for which I received slides: TAP-TB-04-801; TAP-TA97-832; A-29-03989; TD-90-019; A-29-04092; TAP-TA-03-805; TAP-TB00-814; A-29-1984; A-29-1979; A-29-438; A-29-680; A-29-681; A-29-1986; A-29-1977. It is my understanding based on communications provided to me from defense counsel that there were additional study pathology slides located at EPL for studies A-29-439/A-29-1388. However, these studies were not included on the hard drives I received. I reserve my right to review these studies and offer additional opinions, if warranted, in the event these slides are made available to me.

number for which I had requested pathology slides, but these other slides were not made available to me.

1. Review of Takeda Two-Year Non-Clinical Studies

In my review of the documents produced by Takeda relative to the non-clinical studies performed by the company, I reviewed a 1994 summary report entitled A-29-2116: Preclinical Expert Report Lansoprazole (Long-Term Maintenance Treatment) authored by Takeda Consultant in Toxicology Dr. Ralph Heywood, Ph.D. To my understanding, this preclinical expert report was prepared for the purpose of extending the usage of lansoprazole from short-term therapy to long-term maintenance at the dosage of 15-30 mg/day.[5] According to the report, "[t]he animal studies that support long-term therapy are the carcinogenicity studies, for during the course of these studies, standard toxicological parameters were monitored and at termination, detailed study was made of the target organs."[6] Long-term carcinogenicity findings are summarized in this report. I noted the following statement in the report that attempts to explain the kidney pathology findings in the 2-year rat carcinogenicity studies with 7 days a week dosing:

> The severity of nephropathy (CPN), a rat specific lesion showed an increase in comparison with controls in both carcinogenicity as [sic] studies with dosing 7 days a week. This was particularly true with respect to female animals. The nature of the increase was minor as it did not lead to an increase in mortality as a result of renal failure.[7]

Dr. Levin appears to discount the kidney pathology findings observed in the 2-year lansoprazole rat carcinogenicity studies (See Levin Notes at pgs. 3, 5, 8). As such, among other studies, I asked

[5] TAKPPI-MOSAIC-00020777
[6] *Id*.
[7] TAKPPI-MOSAIC-00020792

to review the underlying pathology from the 2-year rat carcinogenicity studies to assess these previous interpretations of renal lesions in dosed animals.

A-29-1977/TA91-024 (R&D/93/546): Two-Year Oral Oncogenicity Study in Rats of Lansoprazole (International Research and Development Corp. Study No. 126-051)

Per the 1994 Preclinical Expert Report, FDA requested TAP Pharmaceuticals to conduct this study at what the FDA considered to be the maximum tolerated dose (MTD).[8] Groups of Sprague-Dawley rats (70/sex/group) received lansoprazole at dosages of 0, 5, 25, 75 or 150 mg/kg/day each day, seven days a week, for two years. Doses were administered by gavage in a vehicle of 5% gum arabic in deionized water.[9]

There were both macroscopic and microscopic findings recorded for the kidneys in the report. Macroscopic observations in the kidney included renal lesions in both males and females such as hydronephrosis (dilated renal pelvis). Study authors concluded that these macroscopic changes were spontaneous and not related to the test article. Microscopic changes in the kidney were identified in the report as being possibly drug-related and increased in incidence and/or severity with increasing dosage level, especially in female rats.[10] In addition, it was noted in the study report that "[t]he incidence of chronic progressive nephropathy (Table 53.2-12) was increased compared to the Vehicle Control A group in the 25, 75 and 150 mg/kg/day female rats."[11] Table 53.2-12 extrapolated from the study report is below:

[8] TAKPPI-MOSAIC-00020779
[9] TAKPPI-MOSAIC-00022435 at pg. 6
[10] TAKPPI-MOSAIC-00022435 at pg. 20
[11] *Id*. at pg. 25.

Table 5.3.2-11

INCIDENCE OF CHRONIC PROGRESSIVE NEPHROPATHY DOS AND TS - FEMALES

Dosage	Vehicle Control A		5 mg/kg		25 mg/kg		75 mg/kg		150 mg/kg	
	DOS	TS	DOS	TS	DOS	TS	DOS	TS	DOS	TS
Number Examined	46	24	27	43	42	28	31	39	28	42
CHRONIC PROGRESSIVE NEPHROPATHY										
- trace	9	8	6	17	9	13	4	10	4	9
- mild	14	4	8	9	22	11	17	22	17	26
- moderate	2	3	2	2	2	1	2	5	4	7
- severe	2	2	2		2		4	1		
TOTAL	27	17	18	28	35	25	27	38	25	42

[12]

The study authors, citing to Bowman, G., et al, (1990) *Nephropathology (CPN) Common Spontaneous Lesions*, Pathology of the Fischer Rat (1), attributed microscopic renal findings in females to chronic progressive nephropathy:

> "Chronic progressive nephropathy" as a "common spontaneous renal lesion in the Sprague-Dawley rat (4), particularly in males."[13]

Dr. Levin addresses this study in his "Notes":

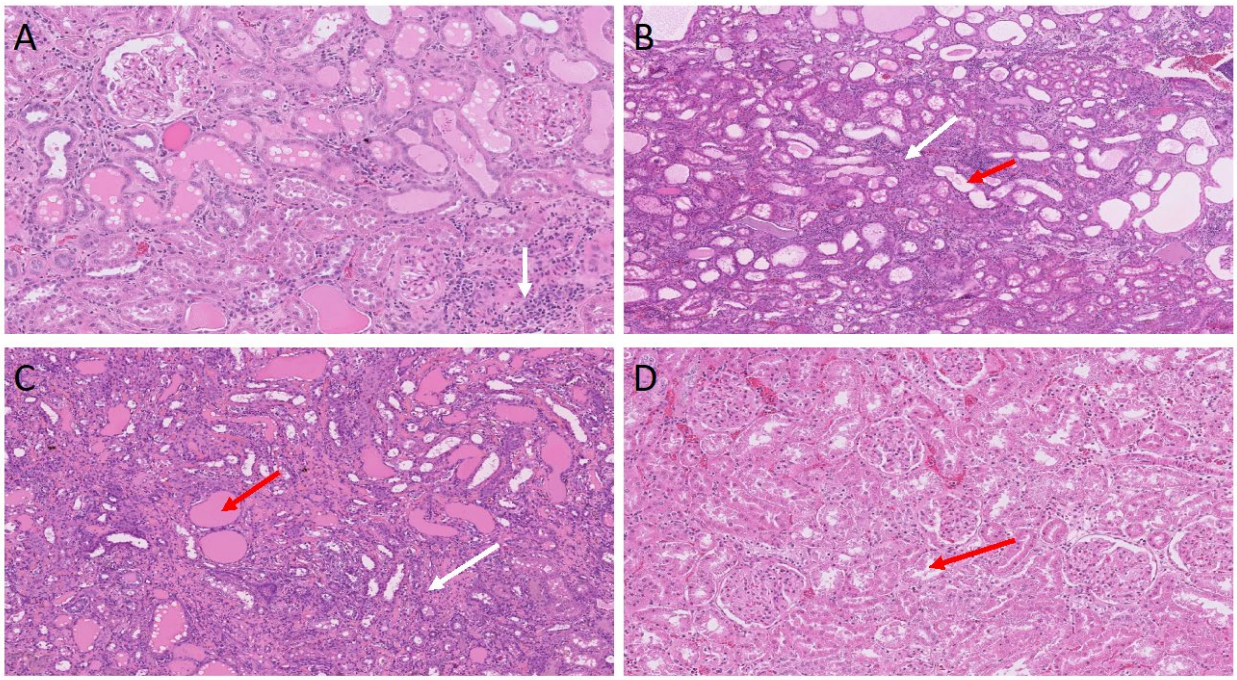
> "The incidences of CPN were reported to be increased compared to controls in female groups at 25, 75 and 150 mg/kg/day (Text table 5.3.2-11 in IRDC report). As the name implies CPN is a progressive disease in rats. It typically is first to detect around 3 months of age in a few rats and its incidence and severity increases with age. So it is not surprising that the incidence of this spontaneous disease would be higher in the groups that had better survival. The severity of CPN in the 150 group was not increased (Table 11), as might be expected if the test-article caused a direct effect on the kidneys."[14]

In addition to my review of the written materials relative to this study, I reviewed actual images of test animals in different dosage groups that the study authors had characterized as having

[12] *Id*. at pg. 36.
[13] *Id*. at pg. 25.
[14] Levin notes at pg. 8.

"chronic progressive nephropathy." As shown below, and pertinent to my own opinions in this case, the lesions in the control group are less severe than in dosed groups.

Fig. 1: Male animal kidneys with "chronic progressive nephropathy"

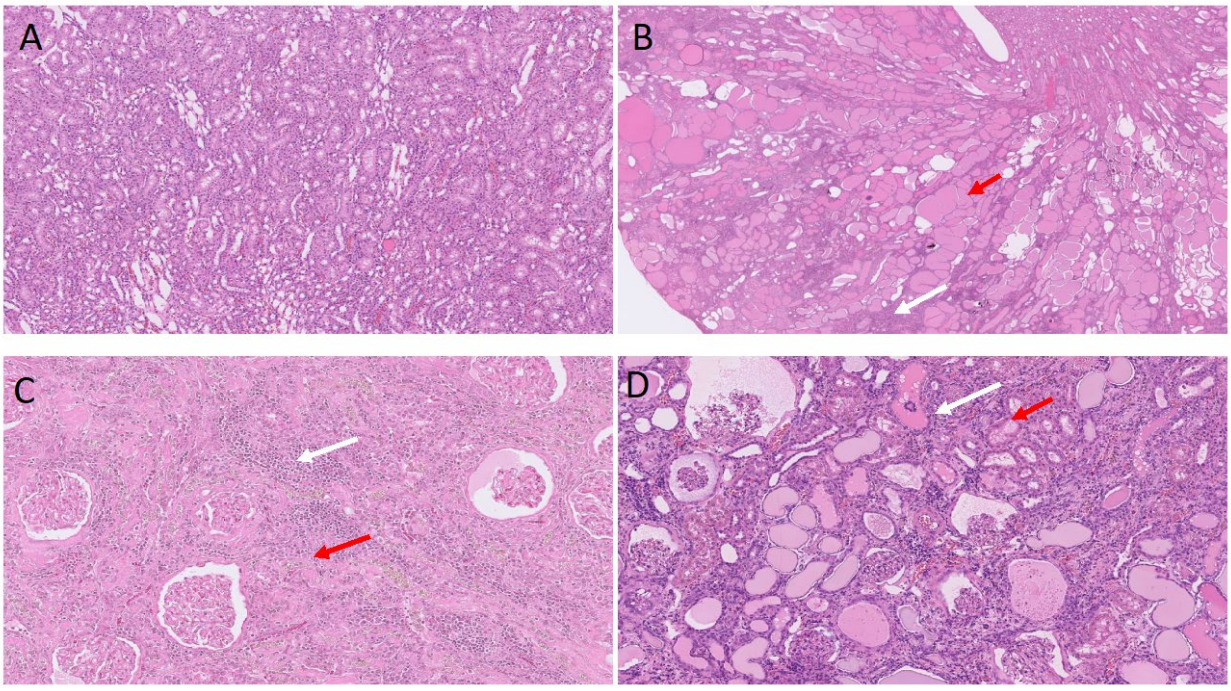


- A: 0 mg/ kg group (#13477).[15]
- B: 25 mg/kg group (#13726).[16]
- C: 75 mg/kg group (#13912).[17]
- D: 150 mg/kg group (#14035).

I observed distinct lesions in these animals. A, B and C show inflammatory infiltrate (white arrows). B, C and D show acute tubular injury (red arrows). However, these differences are not captured by study pathologists who classified each as having some form of spontaneous chronic progressive nephropathy, among other findings.

[15] A-29-1977_TA91-024 Metadata Image Filename: TD91-024;126-051_13477_24 ndpi.
[16] A-29-1977_TA91-024 Metadata Image Filename: TD91-024; 126-051_13726_23 ndpi.
[17] A-29-1977_TA91-024 Metadata Image Filename: TD91-024; 126-051_13912_23.ndpi.

Fig. 2: Female animal kidneys with "chronic progressive nephropathy"



- A: control group (#13513).[18]
- B: 5 mg/kg group (#13667).[19]
- C: 25 mg/kg group (#13789).[20]
- D: 75 mg/kg group (#14072).[21]

I observed well-preserved renal tissue in control females including #13513 as shown above. In contrast, B, C and D showed inflammatory infiltrate (white arrows) and severe acute tubular injury (red arrows). It is clear when comparing slide A with slide D that the lesions in the dosed animal are far more extensive than the fairly healthy control. However, study pathologists diagnosed both animals (13513 and 14072), as suffering from "chronic progressive nephropathy, bilateral moderate."

However, the lesions I observed in dosed groups do not fit within the CPN

[18] A-29-1977_TA91-024 Metadata Image Filename:TD91-024; 126-051_13513_24 ndpi.
[19] A-29-1977_TA91-024 Metadata Image Filename: TD91-024; 126-051_13667_24.ndpi.
[20] A-29-1977_TA91-024 Metadata Image Filename: TD91-024; 126-051_13789_23.ndpi.
[21] A-29-1977_TA91-024 Metadata Image Filename: TD91-024; 126-051_14072_24.ndpi.

definition used by Takeda. What was striking in the review of the kidney tissue sections was the significant increase in extent of tubular injury and inflammatory infiltrate with increased dosage of lansoprazole. That should have raised a concern by the investigators to consider a drug-dependent etiology of the tubular injury and the inflammation that is clearly seen on microscopic inspection. This in turn should have prompted the investigator to recommend that further toxicology studies more focused on the kidney itself be conducted.

A-29-1986/ TD91-276 (R&D/93/731): Two-Year Oral Oncogenicity Study in Mice of Lansoprazole (International Research and Development Corp., Study No. 126-057) [22]

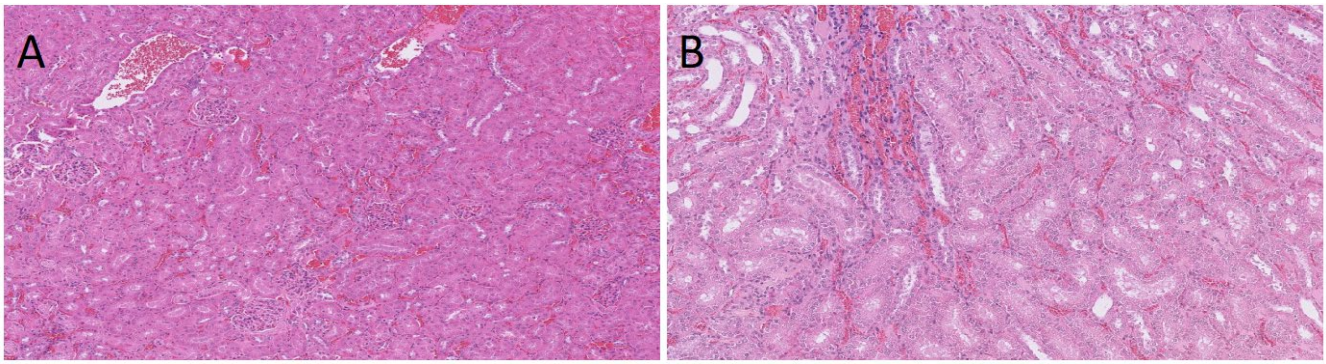
In this 2-year oncogenicity study, Lansoprazole was administered by gavage to young Crl: CD-1 BR mice for approximately two years at dosage levels of 0 and 600 mg/kg/day in 5% gum Arabic vehicle. [23] Dr. Levin concluded that "Neither the report text nor the histopathology incidence Table 9 indicate any test-article related effects on kidney. The diagnostic term 'nephritis, interstitial, chronic' showed no treatment related trends in male or female mice." Pg. 6 of Levin. However, I disagree with Dr. Levin's interpretation of the document. In reviewing the same document, I noted "microscopic observations" recorded in Table 9 for female dosed mice that occurred more often and to a greater degree than the control group. For example, there were 10 more female mice with "nephritis, interstitial, chronic" observations in the test animal group as compared with the control group. Furthermore, descriptions of "moderate" "nephritis, interstitial, chronic" were observed in 29 female mice receiving test article compared to only 7 in the vehicle control group, an incidence rate four times greater in exposed vs. unexposed mice.

Contrary to certain comments that I saw from the examining pathologists, I observed fairly-well preserved kidney tissue in both control animals that allowed for an adequate assessment of

[22] TAKPPI-INDNDA-01620126.
[23] TAKPPI-INDNDA-01620135.

the tissue slides I received. After examining the available mice pathology slides, it is my opinion that dosed mice of both sexes showed more extensive tubular lesions than controls and that these lesions represent lansoprazole-associated renal injury that were not accurately categorized by the reviewing pathologist. (see below)

Fig. 3: Control animals



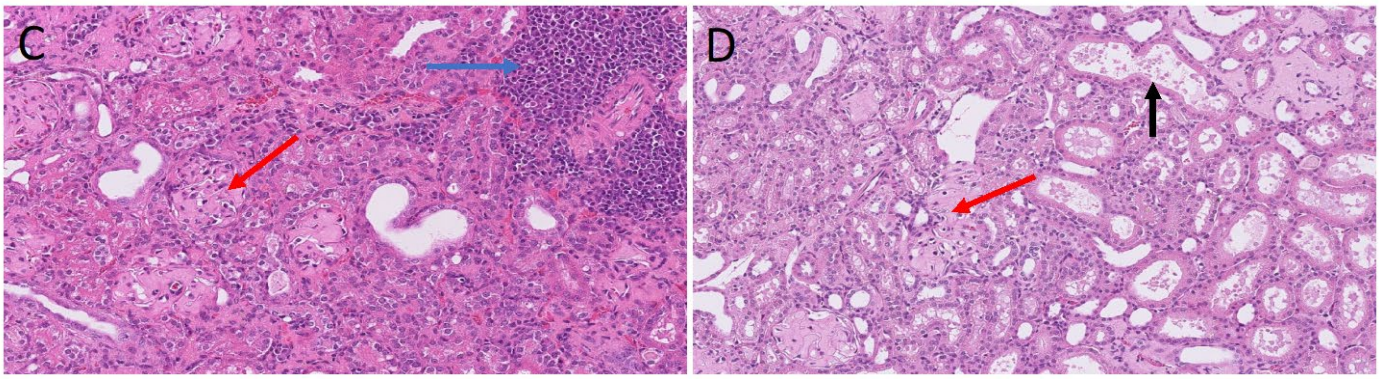
A: control male # 43358[24] B: control female #43418[25]

Control animal #43358: Kidney pathology findings in this control animal are described as "perivascular mononuclear infiltrate, multifocal, bilateral, trace."[26]

Control animal #43418: Study authors recorded kidney pathology findings in this control animal including "amyloidosis, bilateral, moderate" and "nephritis, interstitial, chronic, bilateral, mild."[27]

[24] A-29-1986_TD91-276 Metadata Image Filename: TD91-276; 126-057_43358_21.ndpi.
[25] A-29-1986_TD91-276 Metadata Image Filename: TD91-276; 126-057_43418_22.ndpi.
[26] TAKPPI-INDNDA-01620764.
[27] TAKPPI-INDNDA-01621117.

Fig. 4: Dosed animals



C: male 600 mg/kg group animal #43448[28] D: female 600 mg/kg group animal #43553[29]

- Red arrows show glomerular amyloid.
- Blue arrow shows lymphocytic infiltrate.
- Black arrow shows acute tubular injury.

As shown in the images above, the pathology I observed in dosed animals was more extensive than controls. In my opinion the kidney sections clearly show an increase in interstitial inflammatory infiltrate and tubular injury compared to the control sections. Therefore, it is my opinion that the study pathologist should have attributed these to study-drug induced changes that warranted further investigation. Moreover, in my opinion the kidney tissue control sections were inadequately assessed. My own review showed fairly normal appearance of the control kidney tissue, especially the tubulointerstitial compartment, which differed from the description contained in the study report. In my opinion, this apparent dismissal of kidney lesions present in the dosed groups was erroneous.

A-29-1979/ TD91-025 (R&D/93/547): Two-Year Oral Oncogenicity Study in Mice of Lansoprazole (International Research and Development Corp. Study No. 126-052)[30]

Lansoprazole was administered by gavage once daily to 70 CD-1 mice/sex/group at dosage

[28] A-29-1986_TD91-276 Metadata Image Filename: TD91-276; 126-057_43448_21.ndpi.
[29] A-29-1986_TD91-276 Metadata Image Filename: TD91-276; 126-057_43553_21.ndpi.
[30] TAKPPI-MOSAIC-01307709

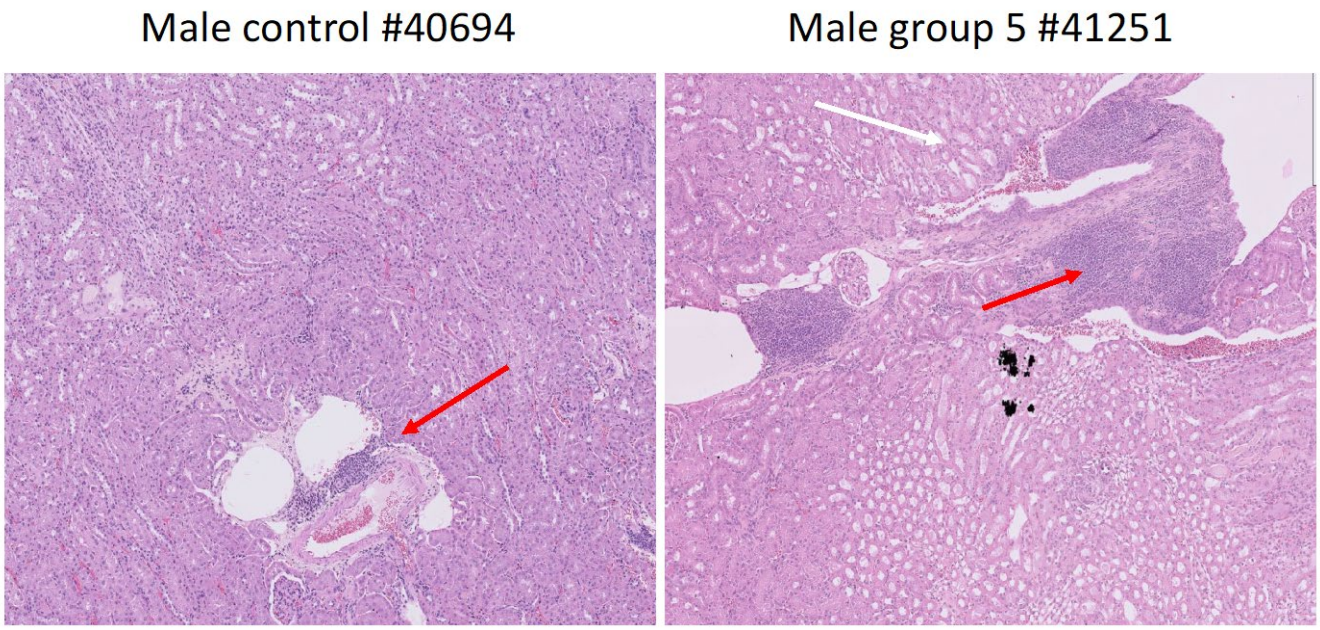
levels of 15, 75, 150 and 300 mg/kg/day 7 days a week for two years. Two control groups each of 70 male and 70- female animals received the vehicle (5% gum Arabic). Drug-related mortality was seen at dosages of 75, 150 and 300 mg/kg/day. Pale, tan, discolored and/or granular kidneys were discovered macroscopically. Investigators deemed these observations typical of spontaneous lesions in mice of this strain" and therefore not drug-related. (pg. 38). Only livers from the females in Vehicle Control B group animals were examined microscopically. (Pg. 29).

Macroscopic observations for male mice that died before unscheduled sacrifices include small, mild kidneys (15 and 75 mg/kg day groups); enlarged, mild and moderate findings in dosed males. Neither vehicle control group had these findings. (Table 9, pg. 140).

There were greater incidences of certain kidney microscopic observations in dosed animals than controls. Pathologists discovered that 2 males (both in 150 mg/kg group) had acute nephritis.[31] This finding was not present in any control group male. None of the control group male animals had this finding. Likewise, 2 mice in 150 mg/kg/day group had necrosis (1 in 400 mg/kg/day group had moderate necrosis). Again, this finding was not observed in controls.[32] Similarly, as is shown in Table 10, there were microscopic observation in female groups that occurred in dosed groups but not in the vehicle control group such as mineralization (1 in 75 mg/kg/day group; 1 in 150 mg/kg/day group; 4 in 300 mg/kg day group), and 1 mouse in every dosed group had dilatation, tubular whereas none of the female controls had this finding.

[31] Pg. 222.
[32] Pg. 183.

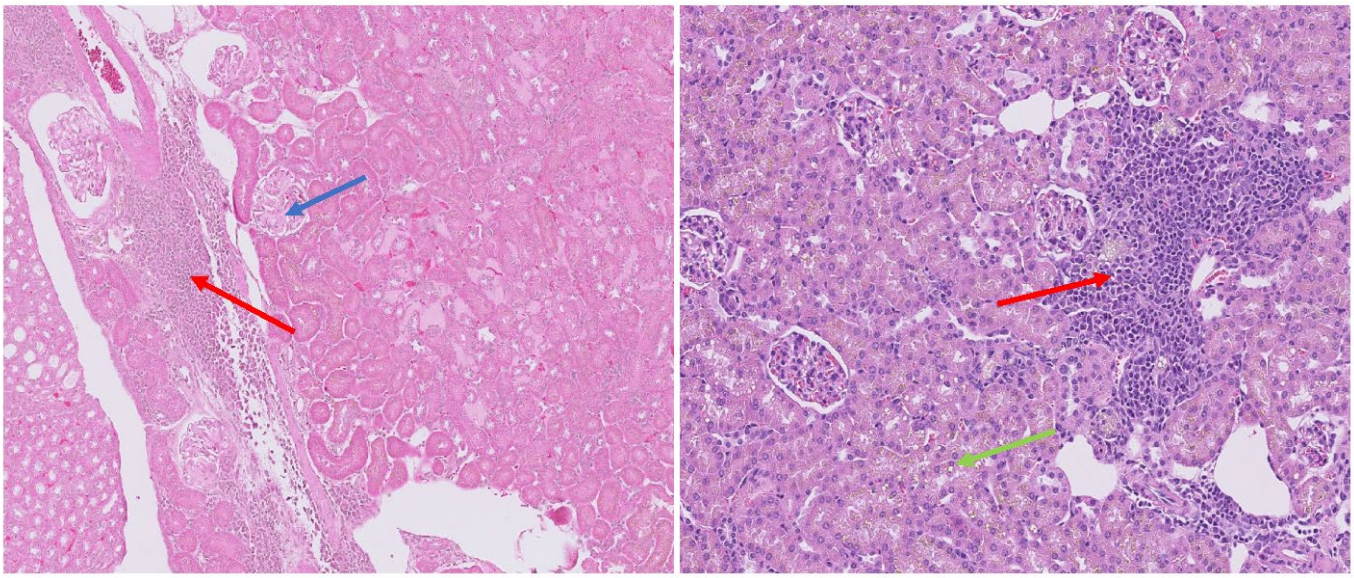
Compound Image 1:[33]



As is shown above, male control shows minimal infiltrate (red arrow, left) while the treated animal shows massive infiltrate (red arrow, right) and extensive tubular injury (white arrow).

[33] Left image: 126-052 Metadata File Name: 40694 21 1M Adult 126-052 3.12.93 TS IRDC - 2021-03-24 13.07.45.ndpi.
Right image: 126-052 Metadata File Name: 41251 21 5M Adult 126-052 3.11.93 TS IRDC - 2021-04-05 16.00.15.ndpi.

Compound Image 2:



Female control 40764[34] Female group 5: 41319[35]

As is shown in compound image 2 above, the female control animal showed focal infiltrate (red arrow, left) and pink, amorphous material (Amyloid) in glomeruli (blue arrow). The female in the dosed group had distinct and more severe pathology. I observed severe inflammatory infiltrate (red arrow, right) and massive amounts of green crystals (green arrow) in tubular epithelial cells in dosed animal #41319.

These differences in pathology are not highlighted in the study report. Study pathologists recorded the same observation for these two female animals: "nephritis, interstitial, chronic, mild." In addition, the control animal was also recorded as having amyloidosis, bilateral moderate. The dosed animal was also recorded as having mineralization, multifocal, bilateral, trace.

[34] 126-052 Metadata File Name: 40764 21 1F Adult 126-052 3.12.93 TS IRDC - 2021-03-19 19.21.30.ndpi
[35] 126-052 Metadata File Name: 41319 21 5F Adult 126-052 3.11.93 TS IRDC - 2021-04-06 15.33.18.ndpi.

In his notes, Dr. Levin represents that no treatment related trends in male or female mice emerged from this study based on the report text and histopathology incidence Table 10.[36] I have reached a different conclusion based on my examination of histopathology slides. The abnormal pathology consistently apparent in dosed mice compared to controls indicates that lansoprazole underpins the development of these renal lesions.

2. Review of Takeda Long-Term Non-Clinical Studies

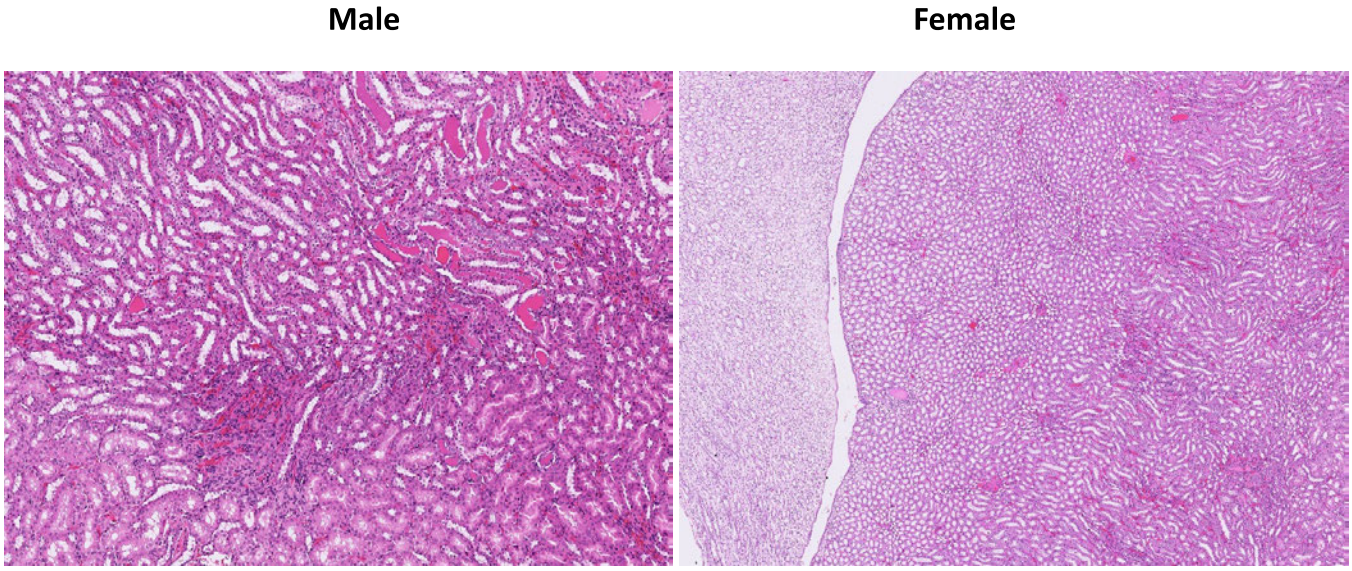
A-29-438 (86-3108): A One Year Oral Gavage Toxicity Study of AG-1749 in Rats[37]

This one-year oral toxicity study was conducted for Takeda to evaluate the toxicity of AG-1749 when administered orally by oral gavage to Sprague-Dawley rats (30/sex/group) at dose levels of 1.5, 5, 15, and 50 mg/kg/day for one year. A control group received the vehicle at the same dose volume as the dosed groups. After at least one year of treatment, all survivors were sacrificed. Histopathological evaluation of selected tissues was only conducted on animals in Groups I and V and on animals from other groups that died before termination of the study.[38]

Compared to the control groups, the animals administered study drug showed significant dose-dependent increase in inflammatory infiltrate and acute tubular injury (ATI). As seen in Figs 2 & 3 below, the extent of tubular injury with cast formation and the interstitial inflammatory infiltrate was extensive in the dosed animals. Moreover, these findings increased significantly from the 1.5mg/kg group to the 50 mg/kg study group. In my opinion the lesions in the kidney tissue were more severe in female animals compared to males. All of these findings point towards drug-mediated kidney injury which should have been clearly documented and further investigated.

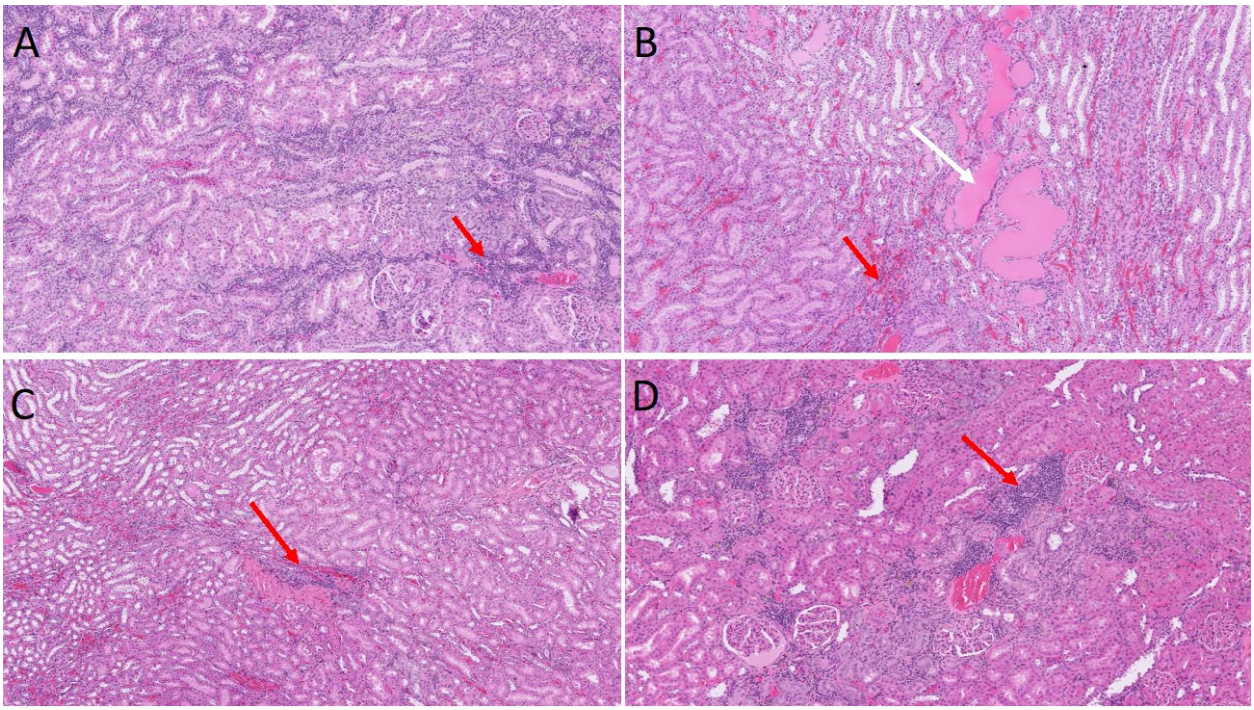
[36] Levin notes at pg. 5.
[37] TAKPPI-MOSAIC-00022786
[38] TAKPPI-INDNDA-01024117

Fig. 5: Kidney tissue sections from group 1: 0 mg/kg AG 1749



- Male (#1026) [39]and female (#1508)[40] kidney tissue sections from group 1: 0 mg/kg AG 1749

Fig. 6: Male kidney tissue sections treated with AG-1749.

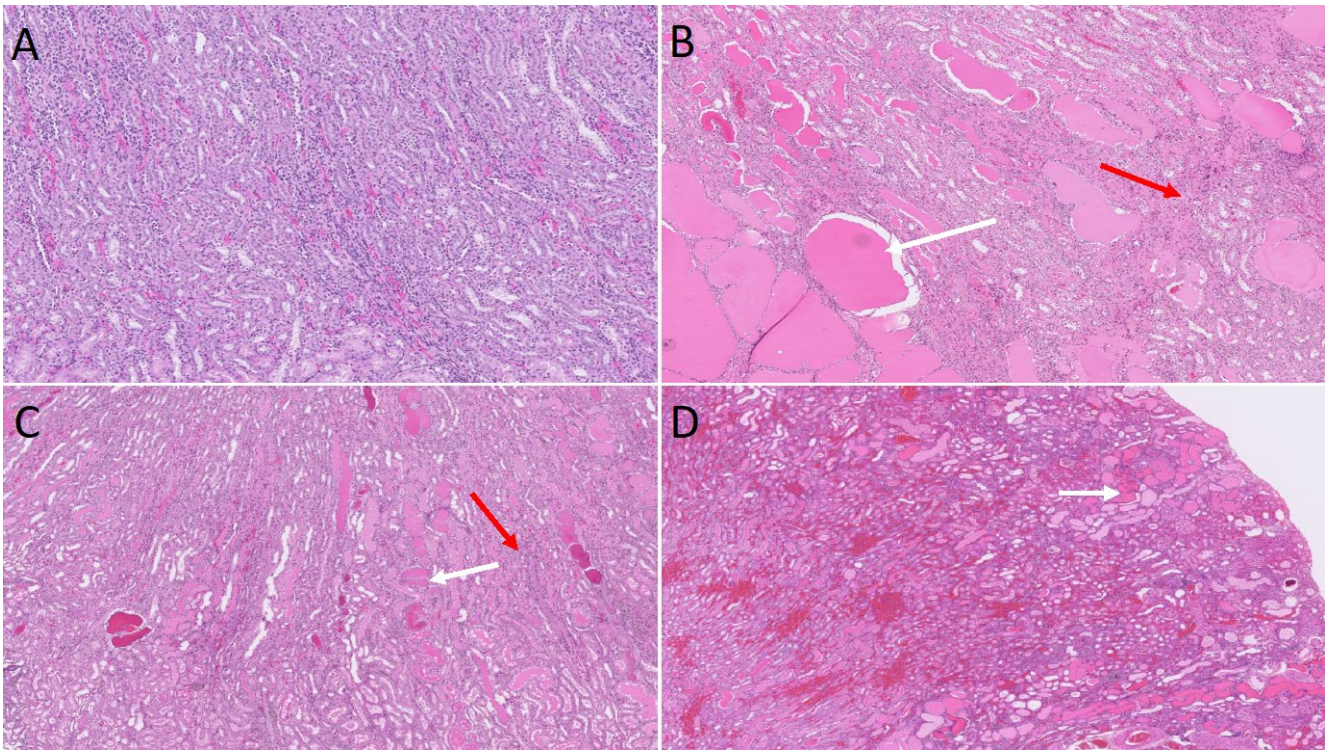


[39] A-29-438_86-3108 Metadata Image Filename: 86-3108_1026_15 ndpi.
[40] A-29-438_86-3108 Metadata Image Filename: 86-3108_1508_15 ndpi.

- A: group 2 (1.5 mg/kg, #2009).[41]
- B: group 3 (5 mg/kg #3026).[42]
- C: group 4 (15 mg/kg #4017).[43]
- D: group 5 (50 mg/kg #5002).[44]

Infiltrate=red arrow; cast=white arrow.

Fig. 7: Female kidney tissue sections treated with AG-1749.



- A: group 2 (1.5 mg/kg #2512).[45]
- B: group 3 (5 mg/kg #3518).[46]
- C: group 4 (15 mg/kg #4505).[47]
- D: group 5 (50 mg/kg #5518).[48]

Infiltrate=red arrow; cast=white arrow.

[41] A-29-438_86-3108 Metadata Image Filename: 86-3108_2009_15 ndpi.
[42] A-29-438_86-3108 Metadata Image Filename: 86-3108_3026_15 ndpi.
[43] A-29-438_86-3108 Metadata Image Filename: 86-3108_4017_15A.ndpi.
[44] A-29-438_86-3108 Metadata Image Filename: 86-3108_5002_15A.ndpi.
[45] A-29-438_86-3108 Metadata Image Filename: 86-3108_2512_15 ndpi.
[46] A-29-438_86-3108 Metadata Image Filename: 86-3108_3518_15 ndpi.
[47] A-29-438_86-3108 Metadata Image Filename: 86-3108_4505_15 ndpi.
[48] A-29-438_86-3108 Metadata Image Filename: 86-3108_5518_15 ndpi.

Despite the aforesaid depictions of renal injury, Dr. Levin dismissed the clear histopathological findings made by the reviewing pathologist and instead substitutes his own opinion as to these findings as per the following statements contained in is Notes:[49]

> "The histopathology data included the term 'chronic interstitial inflammation/ chronic nephropathy.' I take this to mean CPN."

Dr. Levin provides comments on other findings made by the reviewing pathologist, that purport to minimize the renal lesions as not related to the test article:

> The incidence of CPN was *somewhat higher* in the high dose females (25 of 29) compared to the control females (15 of 29) killed at the termination of the study (Table 18). [emphasis added].
>
> The *kidney weights* of the control and high dose males *were comparable* (Table 13) and the incidences of CPN between these groups were *essentially the same* (26 of 28 controls and 27 of 28 high dose) (Table 17). [emphasis added].

In my opinion, the pathological findings in the kidney tissue sections (Figs 2 & 3), i.e., inflammatory infiltrate, tubular casts and signs of acute tubular injury, were misinterpreted as CPN. Rather, these lesions are consistent with typical patterns of drug-induced acute kidney injury. CPN is a chronic, degenerative disease in old rats, that usually manifests with chronic changes of tubular atrophy and glomerulosclerosis. The kidney lesions seen in the animals of the drug groups and shown in figures 6 and 7 are not consistent with CPN. The misinterpretation of the pathology as CPN prevented the study investigators to further examine kidney-specific injury by the study drug.

[49] Levin notes at pgs. 7-8.

3. Review of Takeda 3-Month Non-Clinical Studies

R&D/90/339 (TA90-152): Three-Month Toxicity Study of Lansoprazole Administered Orally to Rats (with a One-Month Recovery Period) [50]

I asked to review the slides from this study because, based on my review of NDA non-clinical documents, it is my understanding that this study is one of, if not the only, study that treated the kidney as a target organ.[51]

This study was conducted for the purpose of determining the toxicologic and pathologic effects of lansoprazole following daily oral administration. There were 5 groups: control; 50 mg/kg/day; 150 mg/kg/day; 300 mg/kg/day; and 600 mg/kg/day. Significant morphologic changes affecting the kidney were evident in this 3-month study of lansoprazole in Sprague Dawley rats.

As is shown in the tabulated summary tables in the report (Tables 17 & 18), treatment-related morphologic changes affecting the kidney were evident at the end of the treatment period. A higher incidence of renal tubular epithelial basophilia and nephritis were found in rats treated with 150 mg/kg/day or more. Mild and multifocal tubular epithelial basophilia were seen more often in the rats given 600 mg/kg/day. For rats that received 150 mg/kg/day (or greater) the incidence of nephritis (males only) and renal tubular epithelial basophilia was greater than for the control rats. Mild and multifocal tubular epithelial basophilia occurred more commonly in the rats given 600 mg/kg/day, "while the change was mainly focal and minimal in the control and other lansoprazole-treated rats." [52]

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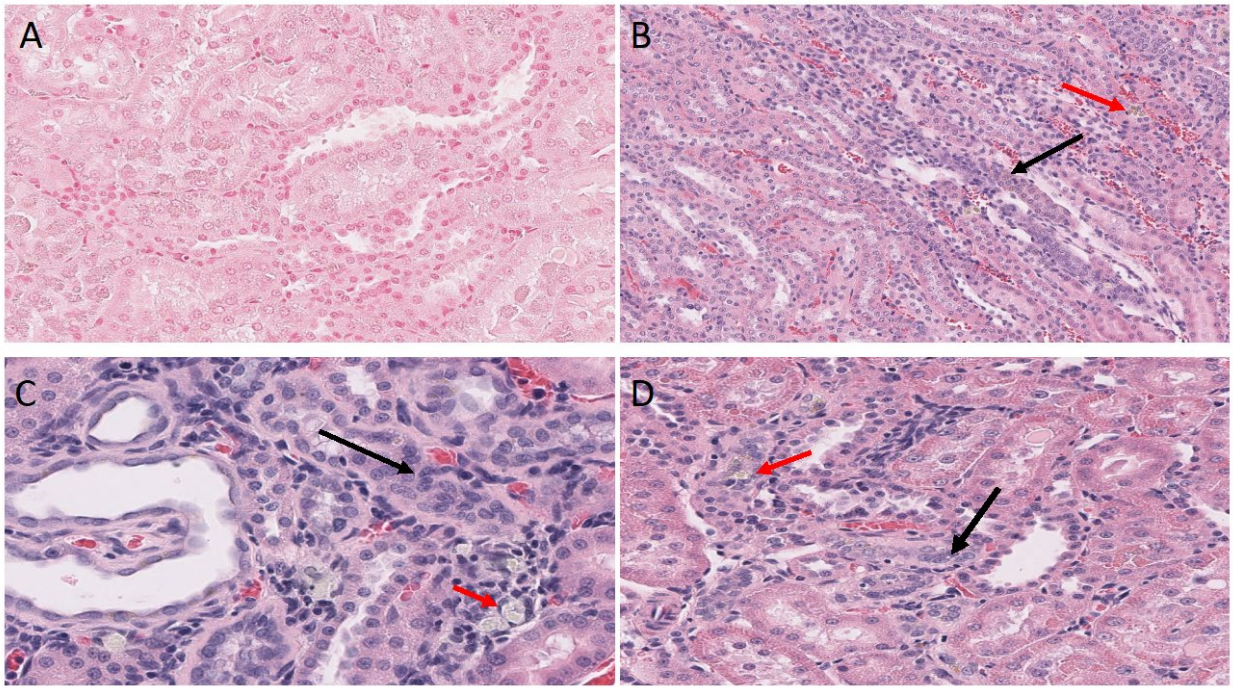
[50] TAKPPI-INDNDA-01045257; TAKPPI-INDNDA-01045753; TAKPPI-INDNDA-01045279

[51] *See* TAKPPI-INDNDA-01147625.

[52] "With the exception of a few high-dosage males in which mild and multifocal chronic nephritis was observed, the inflammatory change in the kidneys from the affected rats was generally minimal and focal in nature. A higher incidence of intraluminal yellow-green and intracytoplasmic yellowish-brown pigmentation that stained negative for iron and bilirubin were also evident in the kidney from rats treated with 150 mg/kg/day or more lansoprazole at the end of the treatment period. The intracytoplasmic yellowish-brown pigment found in the renal tubular epithelial cells was considered to be lipofuscin."

At the end of the recovery period, renal tubular epithelial basophilia and nephritis were still present in the kidneys of some lansoprazole-treated rats.



- A: Control (#1001).[53]
- B (#4011),[54]
- C (#4021)[55]
- D (#4027)[56]

I observed tubular basophilia (black arrow) with small crystals (red arrow) in treatment group with 600 mg/kg Lansoprazole.

I disagree with Dr. Levin's interpretation of these findings because my review of the kidney sections clearly showed tubular basophilia and small crystals with associated inflammatory infiltrate. These findings were not seen in control groups and they indicate a drug-related etiology of the tubular injury and the inflammation. These findings should have led to more detailed studies

[53] T90-152 Metadata File Name: T90-152 A1001 HE.svs.
[54] T90-152 Metadata File Name: T90-152 A4011 HE.svs.
[55] T90-152 Metadata File Name: T90-152 A4021 HE.svs
[56] T90-152 Metadata File Name: T90-152 A4027 HE.svs.

regarding the effect of lansoprazole on kidney tissue in order to obtain a better understanding of renal injuries that were present.

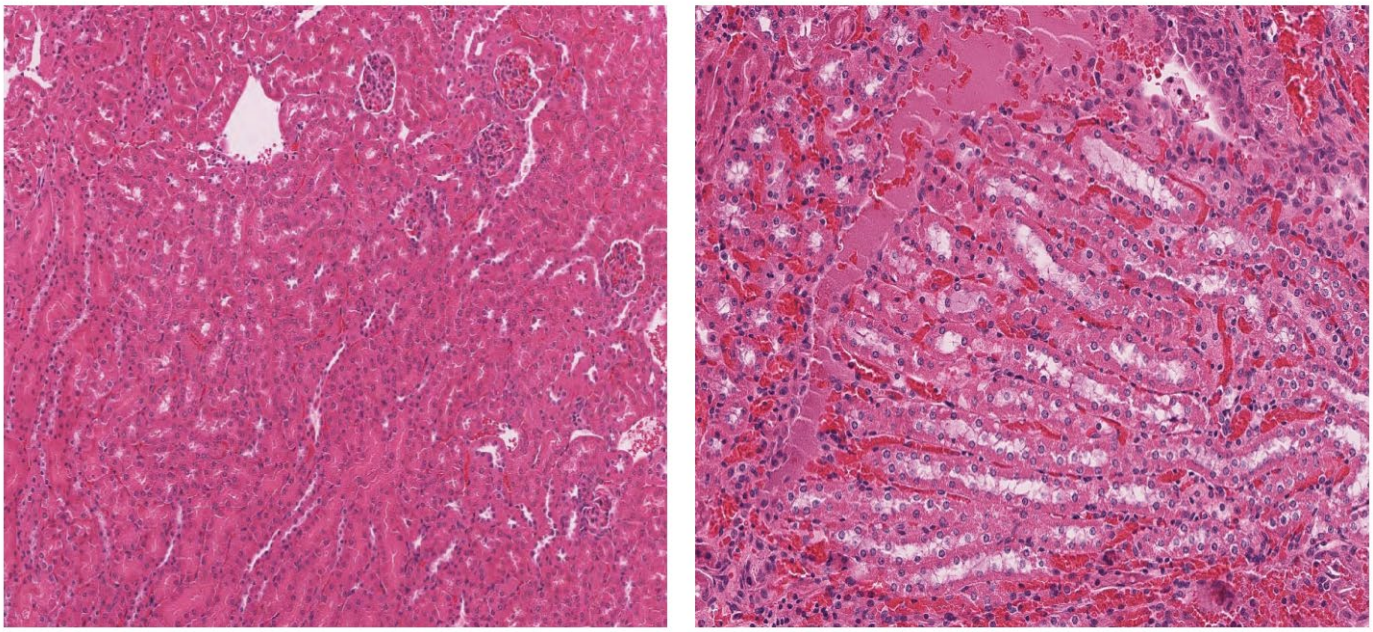
R&D/91/164 (TD90-019): 13-Week Oral Toxicity Study in Mice of Lansoprazole (IRDC Study No. 126-049)

In this study, lansoprazole was administered orally, by gavage, at dosage levels of 150, 300, 500, 1,200 and 2,400 mg/kg/day for 13 weeks to ten CD-1 mice per sex. A control group received the vehicle, deionized water with 5% gum arabic, on a comparable regimen.[57] At necropsy, kidney tissues were harvested from the control and high-dose groups only (Groups 1 and 6, respectively).

During my review of the clinical study report, I noted microscopic pathology findings indicative of acute and chronic kidney injury in the kidneys of male and female mice from Group 6 that prompted me to request the underlying pathology slides. These findings include chronic nephritis, bilateral nephrosis, basophilic tubules, and vacuolation of epithelium in of proximal convoluted tubules. None of these findings were observed in controls. Further, there were 3 drug-related deaths in the highest dosage group that were not assessed by the study investigators. The study authors concluded that "[o]ther microscopic findings in mice from this study were considered spontaneous and unrelated to treatment" and that mice tolerated daily administration by oral intubation of up to 2,400 mg/kg/day."

[57] Beginning on study day 2 and continuing throughout the study, dark blue urine was observed in all treatment groups.

A: animal #39061 **B: animal #39151**

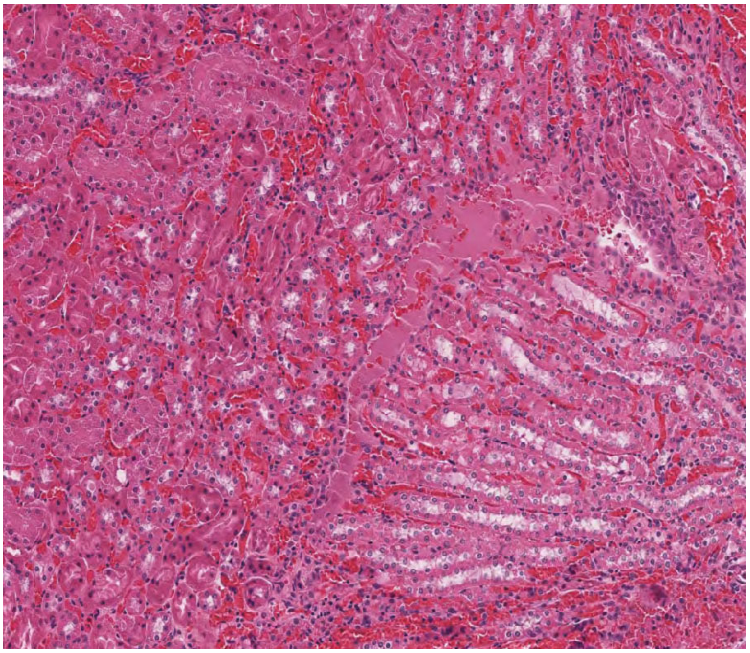


As shown above, the female control animal (#39061 10 1F slide #11) showed well-preserved kidney tissue.[58] In comparison, a representative dosed animal kidney section (# 39151 10 6M) showed tubular basophilia, capillary congestion and proteinaceous exudate with tubular injury. The description provided for this animal in the study report of "nephritis, chronic, unilateral, trace" fails to accurately describe the severity of tubular injury that I observed through my examination.

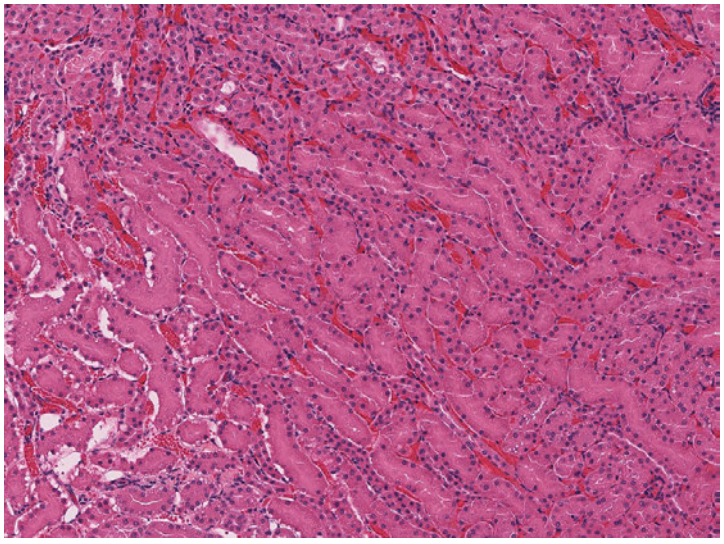
According to Dr. Levin, there were 3 animals in the 2400 mg/kg/day group that were diagnosed with nephrosis (tubule cell vacuolation per animal 39155) and died. Rather than consider the effect of lansoprazole to cause these renal lesions, Dr. Levin indicates that these nephrosis findings could be agonal or postmortem changes. I reviewed these animals with nephrosis diagnoses who died before scheduled termination, and it is my opinion that these animals suffered from drug-induced renal injuries. (see below).

[58] Image A: 126-049 Metadata File Name: 39061 11 1F Adult 126-049 Terminal IRDC.svs.
Image B: 126-049 Metadata File Name: 39151 10 6M Adult 126-049 Terminal IRDC.svs.

#39155[59]



#39169[60]



The kidney injury lesions I detected in my review were not chronic but rather consistent with acute tubular injury due to drug toxicity. Moreover, the lesions were quite extensive and not

[59] 126-049 Metadata File Name: 39155 11 6M Adult 126-049 Terminal IRDC.svs.
[60] 126-049 Metadata File Name: 39169 11 6F Adult 126-049 Terminal IRDC.svs.

"trace" as described in the report. These findings should have led to the conclusion that lansoprazole is the cause of toxic kidney injury in test animals. It is also my opinion that the study investigators misinterpreted the severity and the acute nature of the lesions seen.

A-29-2142 (94026): Thirteen-week Intravenous Toxicity Study of AG-1749 for Injection in Rats[61]

In this study of lansoprazole in Wistar rats, the histopathological examination of the kidneys showed brown pigmentation, tubular basophilia, hyaline casts and focal pyelitis in many study animals. The prevalence of these lesions increased significantly in the higher dose groups (66% of male animals in the 30 mg/kg and 60 mg/kg treatment groups) compared to lower dose groups (40% of male animals in 3 mg/kg treatment group). These findings are indicative of an increase of kidney pathology in dosed groups and should have been followed up with more detailed, kidney specific long-term studies in a larger number of rats.

I was not provided the pathology data for this study as requested. However, I reviewed magnified color images of kidney histology in the affected animals that appeared in the study publication for this report and compared my observations to those of the study pathologists.[62] In my opinion the kidney tissue sections of the treated animals showed much more acute tubular injury (ATI) and acute interstitial nephritis (AIN) than described in the study reports. Photos of renal histopathology slides in dosed animals show findings consistent with tubular injury for which I have extrapolated several images below:

Image **2-38** is from a 60 mg female: "brown pigmentation in the tubular epithelium (minimal)." Some cytoplasmic vacuolization is seen also.

[61] TAKPPI-INDNDA-01201307.
[62] Colored images were produced by Defense counsel in the following Bates: TAKPPI-INDNDA-01833662; TAKPPI-INDNDA-01833663; TAKPPI-INDNDA-01833664; TAKPPI-INDNDA-01833665; TAKPPI-INDNDA-01833666.

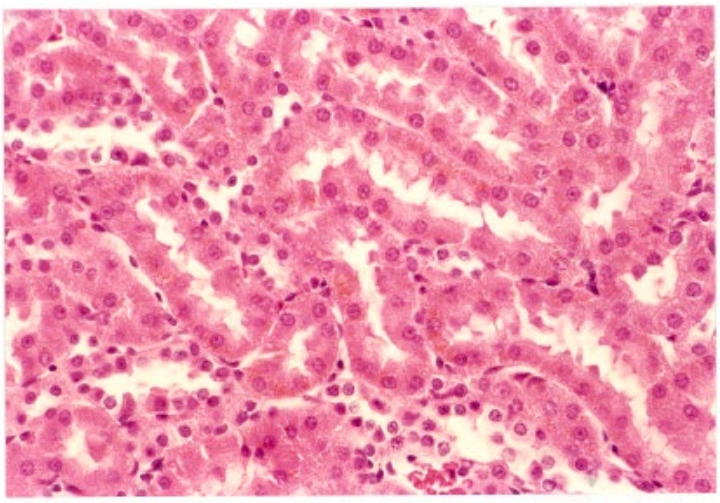


Photo 2-38

As is shown in **Photo 2-39** below, brown pigmentation in the tubular epithelium, tubular dilatation, focal basophilic changes of the tubules, pelvic dilatation and focal pyelitis were observed in a 60 mg male found dead. I also observed brown intra cytoplasmic pigment.

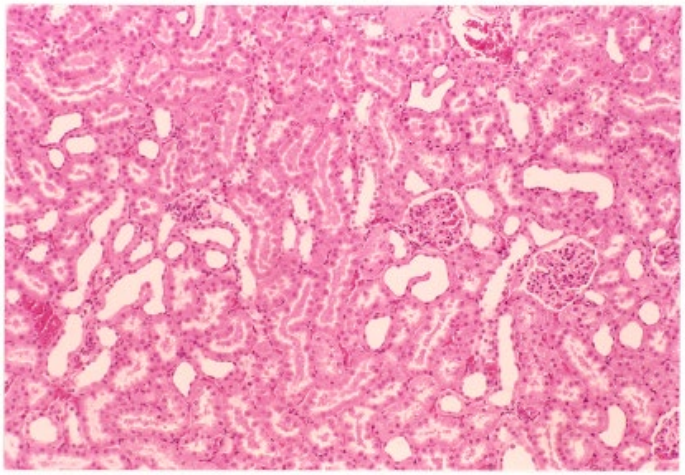


Photo 2-39

Slides from male animal #21 from 3 mg group are shown below.

According to the report- **2-42** shows "focal suppurative nephritis (slight). 2-43: high magnification of the photo 2-42. This animal also had gross findings: Diffuse white spots on kidneys.

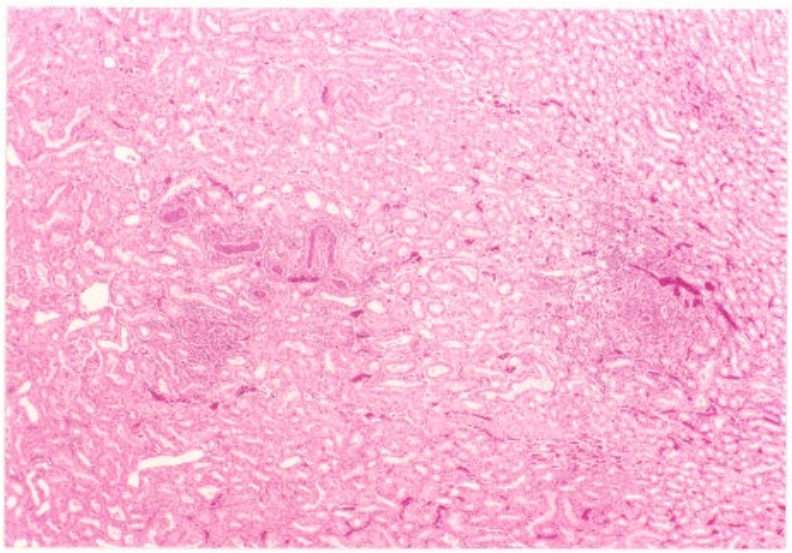


Photo 2-42

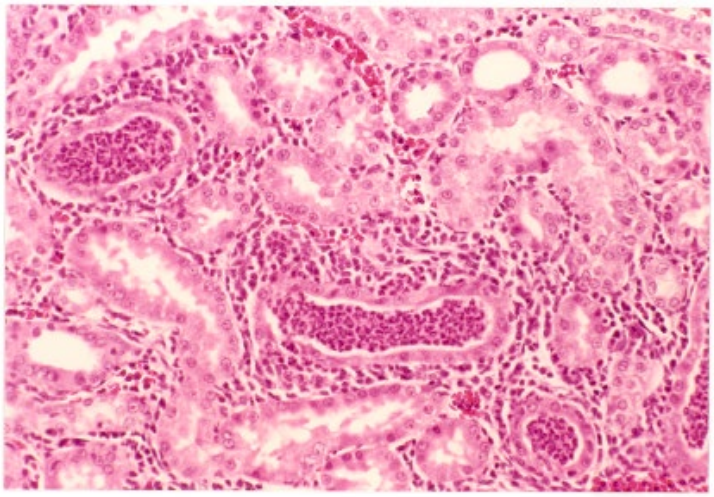
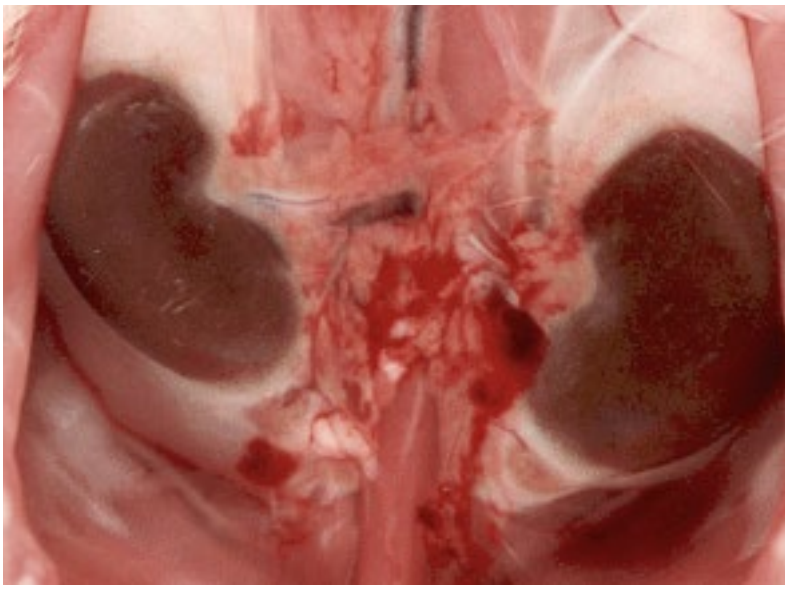


Photo 2-43

Furthermore, diffuse white spots on the kidney, were observed sporadically in dosed rats including 60 mg males as is shown in Photo 1-3 below. These spots represent areas of fibrosis characteristic of CKD in rodents.



It is my opinion that the above represent pathological changes that are consistent with a classic drug-induced tubular injury.[63] These findings raise significant doubt that the tissues were reviewed by a competent renal pathologists. Furthermore, the exposed animals suffered from significantly more adverse events compared to controls. It is my opinion that these findings suggest toxic tubular injury akin to acute renal failure and chronic kidney disease.

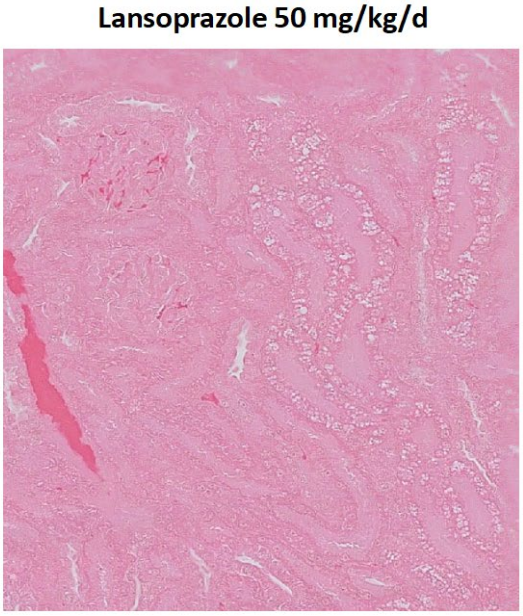
774-010 (TAP TB00-814): A 3-Month Oral Toxicity Study in Preadolescent Dogs using Lansoprazole

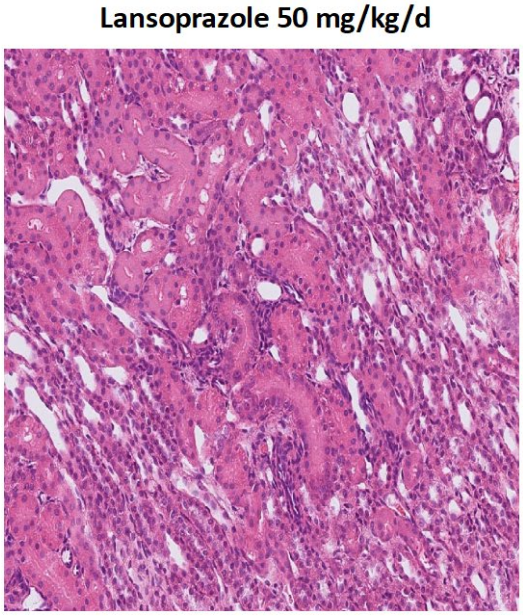
This study was conducted to evaluate the toxicity of Lansoprazole when administered orally to juvenile beagle puppies beginning at 14 days of age for 3 months.[64] 8 puppies/sex/group were dosed as follows: group 1 (control: 0 mg/kg/day); group 2 (5 mg/kg/day); group 3 (15 mg/kg/day); group 4 (50 mg/kg/ day). Test article-related microscopic changes were observed in the kidneys of dosed animals. These findings were characterized as "vacuolar change, fatty" in

[63] TAKPPI-INDNDA-01833664.
[64] TAKPPI-INDNDA-00479099 (pg. 8)

kidneys of male and female puppies administered 50 mg/kg/day.[65] The study authors failed to investigate the significance of these findings and instead state: "[a]lthough test article-related microscopic changes were seen in the kidney and liver, the higher organ to body weight ratio or lower absolute weight seen in the kidney and/or liver suggested a secondary effect due to body weight loss."[66]

After reviewing the slides from this study, it is my opinion that these findings were not correctly interpreted. Rather, the findings are more properly characterized as tubular injury (see below).





The left image shows tubular injury and vacuolization (#157).[67] The right image shows acute tubular injury and basophilic dysplasia (#159).[68]

[65] *Id*. at pgs. 26 and 27.
[66] *Id*. at pg. 25.
[67] 774-010 Metadata File Name: 774-010 MPI 157 3 4F - 2021-03-22 20.19.03 ndpi.
[68] 774-010 Metadata File Name: 774-010 MPI 159 3 4F - 2021-03-22 20.25.52 ndpi.

In my review I found that lansoprazole caused significant injury as manifested by cytoplasmic vacuolization in proximal tubule (left image). Moreover, several areas of kidney injury also showed tubular epithelial cell basophilia, which was not seen in controls. These findings should have raised the suspicion of lansoprazole-dependent tubular injury, especially since cytoplasmic vacuolization is a well-known finding in acute drug toxicity of other medications, such as cyclosporine or contrast media. (2,3). These findings should have raised the suspicion of the investigators to conduct further and more detailed drug-toxicity studies aimed at elucidating harmful effects of lansoprazole on the kidneys of test animals.

4. Review of Takeda Acute Non-Clinical Studies

TAP-TA-03-805 (900285 CTBR): A Four-week Oral (Gavage) Toxicity Study of Lansoprazole in Neonatal Rats Followed by Three Months of Recovery[69]

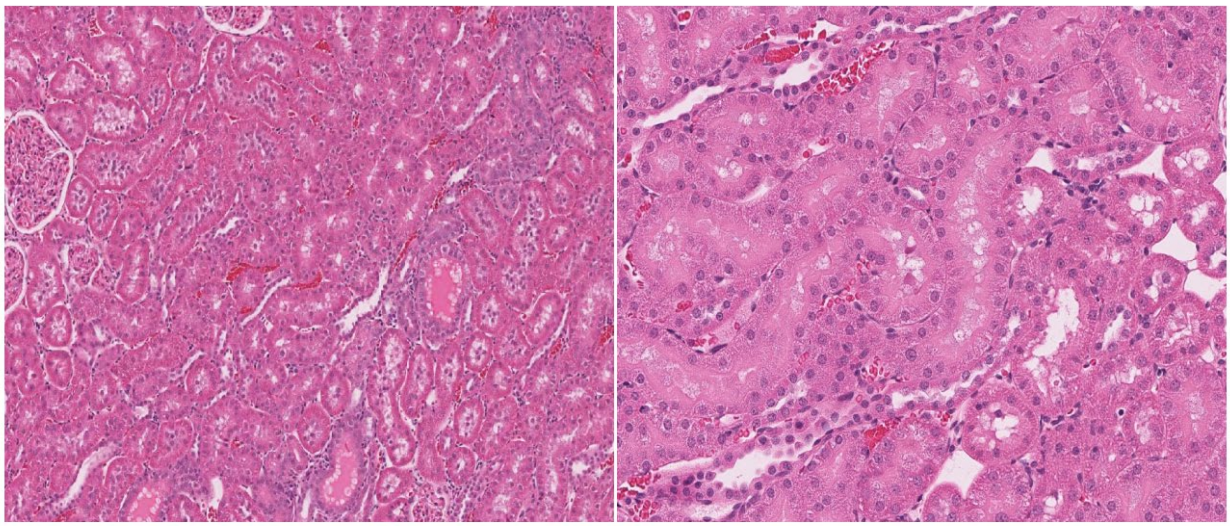
This study was conducted to determine the potential toxicity of lansoprazole when administered by oral gavage to neonatal, weanling, and juvenile rats for 4 consecutive weeks followed by a 13-week recovery period.[70] Dosages of 0, 1.5, 5, 15 and 50 mg/kg/day were used.

Investigators concluded that "[n]o treatment-related gross changes were seen at necropsy either at termination or following the 13-week recovery period. All findings were considered incidental in nature and belong to the usual range of background changes seen in the age and strain of rats examined."[71]

I reviewed male and female control animal slides. These animals showed minimal kidney abnormalities (see below).[72]

[69] TAKPPI-SHRPNT-00711230.
[70] *Id*. at pg. 10.
[71] *Id*. at pg. 31.
[72] TAP-TA-03-805, 900285 CTBR Metadata File Name: 900825 1413-04 1021 3 CTBR.svs (male); TAP-TA-03-805, 900285 CTBR Metadata File Name: 900825 1558-04 1534 3 CTBR.svs (female).

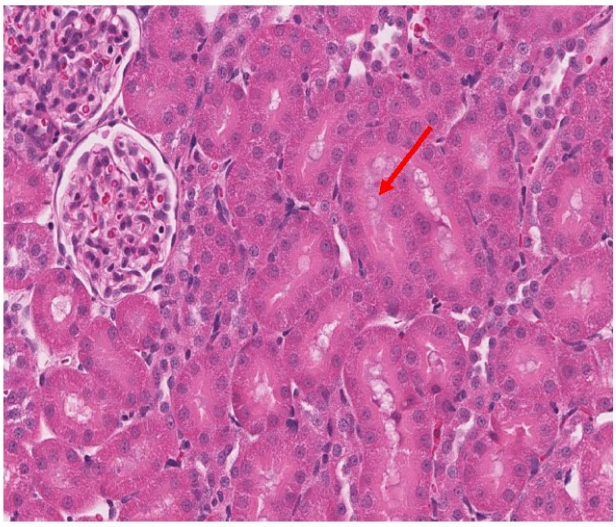
Male control #1021 Female control #1534



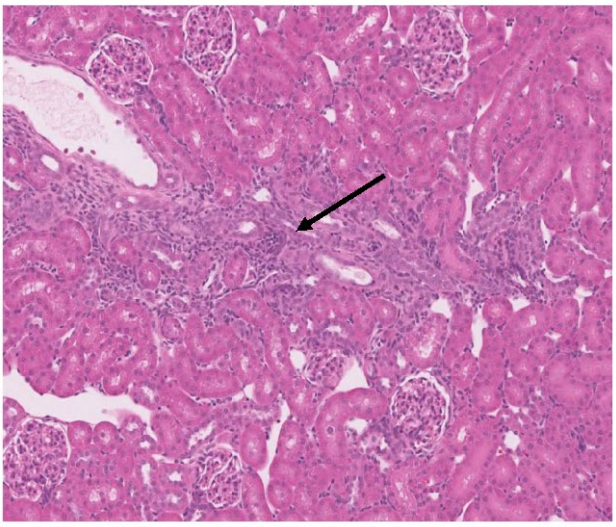
In the study, both animals are diagnosed as having "chronic progressive nephropathy." Specifically, animal 1021 is recorded as having "Chronic progressive nephropathy, bilateral, grade 1; Dilatation: pelvis, unilateral, grade 1.[73] Whereas animal 1534 is diagnosed as having "Chronic progressive nephropathy, focal, unilateral, grade 1.[74]

[73] TAKPPI-SHRPNT-00711230 at pg. 1819
[74] *Id*. at pg. 1828.

Female dosed #5524



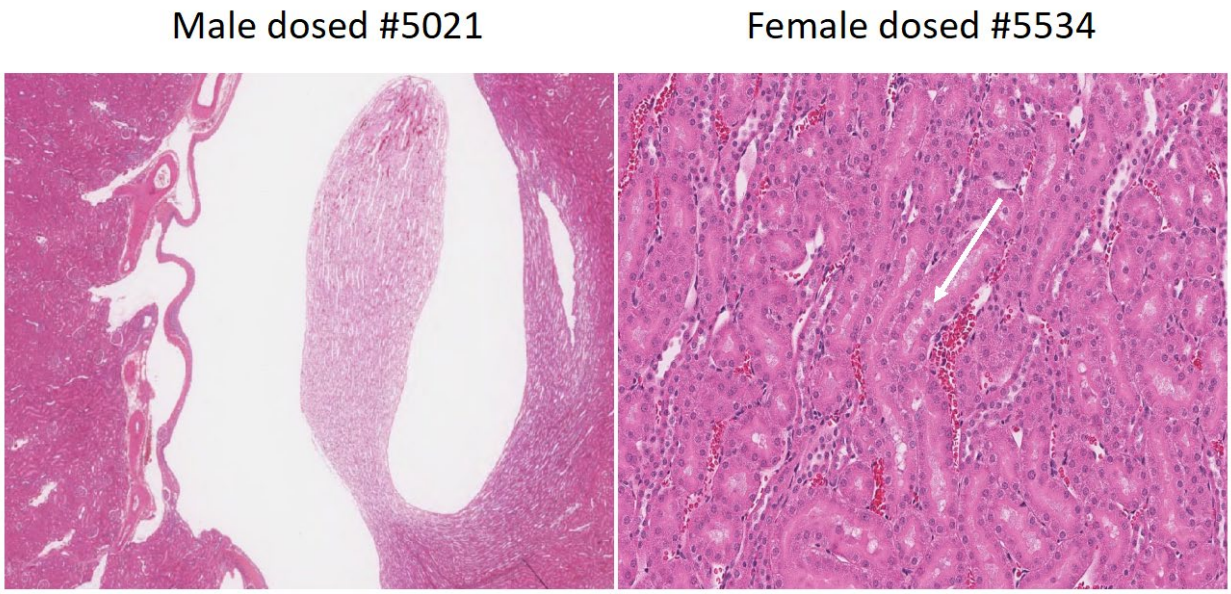
Female dosed #5553



I consistently discovered lesions in dosed females in this study, as shown by representative images above.[75] These female dosed animals showed tubular vacuoles (red arrow, left) and focal basophilia (black arrow, right). No kidney findings are reported for either of these dosed animals in the pathology report.[76,77]

[75] #5524: TAP-TA-03-805, 900285 CTBR Metadata File Name: 900825 1668-04 5524 3 CTBR.svs.
#5553: TAP-TA-03-805, 900285 CTBR Metadata File Name: 900825 1682-04 5553 3 CTBR.svs
[76] TAKPPI-SHRPNT-00711230 at pg. 1798.
[77] *Id*. at pg. 1805.

Other dosed animals showed signs of tubular injury (see below).[78]



Male dosed animals showed obstruction (left) and female dosed animals showed focal tubular injury (white arrow, right). 5021 was not submitted for histopathological examination, and pathologists only recorded 5534 as having "basophilia: tubular, focal, unilateral, grade 1."[79,80]

ANALYSIS

As discussed above, I discovered kidney findings in several species of dosed animals in the Takeda studies for which I was provided pathology slides. These findings mostly consisted of acute tubular injury, inflammatory interstitial infiltrate, tubular cast formation and glomerular amyloid deposits representing kidney tissue damage at various stages of injury. Moreover, several of the animals in different Takeda studies showed extensive green, intratubular crystal deposits.

[78] #5021: TAP-TA-03-805, 900285 CTBR Metadata File Name: 900825 1526-04 5021 3 CTBR.svs.
#5534: TAP-TA-03-805, 900285 CTBR Metadata File Name: 900825 1673-04 5534 3 CTBR.svs.
[79] TAKPPI-SHRPNT-00711230 at pg. 1897.
[80] *Id*. at pg. 1905.

These findings, many of which were dosage-dependent, are indicative of direct drug toxicity to the kidneys in the form of acute tubular injury or tubulointerstitial nephritis.

These findings are consistent with drug-induced kidney injury pathology in human kidney biopsies. It is well-established that inflammatory interstitial infiltrate represents morphologic features of acute tubulointerstitial nephritis in humans. Early drug-induced kidney damage shows infiltration of inflammatory cells and, if the process of damage continues without removal of the offending agent, then the renal interstitial infiltrate becomes more diffuse. (4). As renal damage progresses, tubular cell necrosis, tubular atrophy, and loss of tubules can be seen in human biopsies. (5–7). Likewise, tubular crystalline deposition is an established marker of kidney injury produced by nephrotoxic agents such as anesthetic drugs methoxyflurane and halothane and antiretroviral medications. (8–10). Therefore, I disagree with Dr. Levin's representations that there was no evidence of kidney toxicity in Takeda animal studies that is relevant to clinical use of lansoprazole and dexlansoprazole.

I also disagree with Dr. Levin's apparent dismissal of kidney findings in TA90-152, the one study that examined the kidney as a target organ. According to Dr. Levin, "The kidney findings were probably secondary to pathophysiological effects on general homeostasis. In any event the changes were those of CPN, which has no human counterpart and is considered irrelevant to assessment of human safety." Literature cited by Dr. Levin does not support the theory that renal lesions in dosed animals are of a spontaneous, age-related etiology. Per Barthold, the earliest discernable microscopic change in young rats with CPN is thickening of glomerular basement membranes. (11). Tubular findings in rats *without any significant basement membrane thickening* is associated with acute toxic injury not CPN and should be classified as such. (12).

The overriding theme in Dr. Levin's notes that CPN is at the root of all abnormalities seen in study animals is misplaced. I observed both in the descriptive histopathology as well as through my own microscopic examination of the histopathology in the kidney sections of the non-clinical studies, that the lesions induced by the study drugs were both dose-dependent and acute lesions. Simply stated, the CPN theory fails to explain the distinct findings I observed in dosed animals in the studies reviewed. My findings were not those of CPN, but rather acute tubular injury and interstitial inflammation in addition to other lesions as described above. It is my opinion that Takeda pathologists misinterpreted the kidney findings from animal studies and in so doing missed important signals of nephrotoxicity apparent in various animal models.

CONCLUSION

It is my opinion as a pathologist and clinician that the lesions I observed in PPI-exposed animals in Takeda animal studies are similar to drug-induced lesions in humans. Based upon my review of the studies discussed above, other studies summarized in the attached appendices, and my examination of the provided Takeda histopathology slides, it is my opinion with reasonable scientific certainty that the studies conducted by and for Takeda demonstrated the presence of toxic tubular injury from PPIs.

I reserve my right to supplement this report and my opinions in the event that additional information becomes available to me.

Gilbert W. Moeckel M.D., Ph.D., FASN

Dated: 5/20/2021

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12. Seely JC, Hard GC, Blankenship B. Chapter 11 - Kidney. In: Suttie AW, editor. Boorman's Pathology of the Rat (Second Edition) [Internet]. Boston: Academic Press; 2018 [cited 2021 May 20]. p. 125–66. Available from: https://www.sciencedirect.com/science/article/pii/B9780123914484000113.

APPENDIX A

Additional Takeda Studies: Renal Slides Produced

Rat

Less than one month:

- *Summary of observations: occasional animals show peri-tubular capillary congestion and acute tubular injury (animal#6247 and #6250).*

    a. TAP-TA97-832: Oral Gavage Toxicity Study with Lansoprazole in Preadolescent Rats

Longer than 1 year:

- *Summary of observations: severe extensive injury with acute tubular injury; nuclear drop out; congestion; cytoplasmic vacuoles; focal cortical necrosis; congestion; extensive basophilia; casts; focal calcifications; lymphocytic infiltrate*

    a. A-29-681 (86-3028)[1]: A Two-Year Oral Gavage Oncogenicity Study of AG-1749 in Rats

Mouse[2]

Longer than 1 year:

- *Summary of observations: While I did observe evidence of tubular injury in some control animals, the injury in control animals was very mild and very focal. Compared to controls, the groups 3 and 4 animals showed much more severe tubular injury with cell necrosis and nuclear drop out and sloughed off epithelial cells and tubular cast formation. In group 4 there was also extensive interstitial inflammatory infiltrate. I do note the presence of amyloid deposits within the different groups including controls with greater deposits seen in the group 3 and 4.*

    a. A-29-680 (87-3158): An Eighteen Month Oral Gavage Oncogenicity Study of AG-1749 in Mice.[3]

Dog

Less than one month:

- *Summary of observations: Minimal injury in most kidney sections of dosed groups*

    a. TAP-TB-04-801 (6764-342): Intravenous Bolus and Infusion Toxicity and Toxicokinetic Study with Lansoprazole in Dogs

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[1] I agree with Dr. Heywood's statement that a major deficiency in the study was that lansoprazole was dosed only 5 days a week. TAKPPI-MOSAIC-00020778.

[2] It is my understanding that the metadata spreadsheets provided to me by Defendants for A-29-03989 and A-29-04092 are incorrect. I was unable to match up the study numbers in the report with those on the excel spreadsheets.

[3] I agree with Dr. Heywood's statement that a major deficiency in the study was that lansoprazole was dosed only 5 days a week. TAKPPI-MOSAIC-00020778.

APPENDIX B

Takeda Studies: Renal Slides Requested but Not Received

STUDY TITLE	SPECIES	DURATION	RELEVANT EXCERPTED KIDNEY PATHOLOGY FINDINGS AS DESCRIBED IN STUDY REPORTS

A-29-168 (316/SU):
 	
Thirteen-week Oral Toxicity Study of AG-1749 in Rats [1]
	Wistar rats	13 weeks	-This study is included in Dr. Levin's notes.[2]
			
			- Examples of kidney pathology findings in dosed groups that were greater than controls:
			
			Table IX Histopathology[3]
			
			- Males
			  o Hyaline cast:
			  ▪ Group 1: Slight finding in 1 animal;
			  ▪ Group 2: slight flighting in 1 animal; very slight findings in 2 animals;
			  ▪ Group 3: slight findings in 2 animals;
			  ▪ Group 4: slight finding in 1 animal; very slight finding in 1 animal
			- Females:
			  o Dilatation of tubule:
			  ▪ Group 1: 0 findings
			  ▪ Group 2: slight findings in 2 animals;
			  ▪ Group 3: moderate finding in 1 animal
			  o Hyaline cast:
			  ▪ Group 1: 0 findings
			  ▪ Group 3: slight finding in 1 animal
			  o Calcium deposition:
			  ▪ Group 1: 0 findings
			  ▪ Group 2: very slight finding in 1 animal; slight finding in 1 animal

[1] TAKPPI-INDNDA-01282051
[2] "Notes on lansoprazole and dexlansoprazole nonclinical toxicity studies." at pg. 6.
[3] TAKPPI-INDNDA-01282266- TAKPPI-INDNDA-01282268

STUDY TITLE	SPECIES	DURATION	RELEVANT EXCERPTED KIDNEY PATHOLOGY FINDINGS AS DESCRIBED IN STUDY REPORTS
A-29-174 (Project No. 85-2992): A Three-month Oral Gavage Range-Finding Study of AG-1749 in Rats[4]	Sprague-Dawley rats	3 months	- This study is included in Dr. Levin's notes.[5] - Examples of kidney pathology findings in dosed groups that were greater than controls: Incidence summary[6] - Males: o Bilateral chronic interstitial inflammation: 3/15 in control group; 7/15 in group 5 - Females: o Bilateral chronic interstitial inflammation: 4/15 in control group; 6/15 in group 5
A-29-345 (Project No. 86-3126): A Six-Month Oral Gavage Toxicity Study of AG-1749 in Rats[7]	Sprague-Dawley rat	6 months	- This study is included in Dr. Levin's notes.[8] - Examples of kidney pathology findings in dosed groups that were greater than controls: Incidence summary[9]: - Males: o Bilateral chronic interstitial inflammation ▪ 3/12 control group; 6/12 in group 4 o Bilateral chronic nephropathy ▪ 2/12 in control group; 2/2 in group 3; 4/12 in group 4

[4] TAKPPI-MOSAIC-00022451.
[5] "Notes on lansoprazole and dexlansoprazole nonclinical toxicity studies." at pg. 6.
[6] Pgs. T 17-B-2; T 17-B-3; T 18-B-2; T 18-B-3.
[7] TAKPPI-MOSAIC-01111145.
[8] "Notes on lansoprazole and dexlansoprazole nonclinical toxicity studies." at pg. 7.
[9] Pgs. 1-100; 1-109.

STUDY TITLE	SPECIES	DURATION	RELEVANT EXCERPTED KIDNEY PATHOLOGY FINDINGS AS DESCRIBED IN STUDY REPORTS
			○ Bilateral convoluted tubular epithelium: intracytoplasmic: 3/12 in control; 5/12 in group 4 - Females ○ Bilateral chronic interstitial inflammation ▪ 1/12 in control group; 5/12 in group 4 ○ Bilateral chronic nephropathy ▪ 0/12 in control group; 3/12 in group 4
A-29-1863 (1148/CA): A Twenty-Four-Month Oral Oncogenicity Study of AG-1749 in Rats[10]	Sprague-Dawley rat	104 weeks	- This study is included in Dr. Levin's notes.[11] - Nephropathy was more prominent in the 50 mg/kg groups of both sexes relative to the control groups[12]
AG-1749-15367: Eight-Week Oral Gavage Developmental Bone Toxicity Study of AG-1749 in 7-day-old Rats with a 4-Week Recovery Period[13]	Sprague-Dawley rat (juvenile)	8 weeks	- I asked to review the slides from this study because of histopathological findings in young animals including: ○ Table 15-9 Histopathological findings in male rats [H.E. staining] (End of the dosing period): dilatation renal pelvis findings in dosed animals[14] ○ Table 15-17 Histopathological findings in female rats [H.E. staining] (End of the dosing period): tubular basophilia findings in dosed animals[15]

[10] TAKPPI-INDNDA-01081077; TAKPPI-INDNDA-01080582.
[11] "Notes on lansoprazole and dexlansoprazole nonclinical toxicity studies." at pg. 8.
[12] The original study report for A-29-1863 was amended to add histopathological findings in the kidney that were not included in the original report. The original report represented that: "The most frequent finding was nephropathy in male animals." This sentence was deleted in the second amendment. Nephropathy was prominent in both male and female rats in 50 mg/kg group compared to controls. TAKPPI-INDNDA-01081081.
[13] TAKPPI-INDNDA-00201527.
[14] Pg. 162.
[15] Pg. 170.

B-5278: Thirteen-week oral gavage toxicity study of TAK-390 in rats[16]	Wistar rat
	
	(5 weeks of age)
		13 weeks	- This study is included in Dr. Levin's notes.[17]
			
			- Table 9: Gross pathological findings[18]
			  o Females: dilatation, pelvis findings in dosed groups .
			- Table 10-2: Histopathological findings[19]
			  o Males: urinary cast findings in dosed group

14-091/SU: Four-Week Oral Gavage Toxicity Study of TAK-390 U-X in Rats [20]	Sprague-Dawley rat (6 weeks old at start of dosing)	4 weeks	- On histopathological examination, minimal to mild hyaline droplets of the renal tubules in the kidney were observed in both the TAK-390 alone group and the combination group. The finding in the kidneys was judged to be "toxicologically significant." [21] - Hyaline droplets in the renal tubules were noted as test-article-related abnormalities. [22]
17-006-tk: Range-Finding Toxicokinetic Study of AG-1749 after Oral Administration for 6-weeks in Juvenile Rats[23]	Juvenile Male Sprague-Dawley rat (7 days old at the start of dosing)	6 weeks (42 days)	- Macroscopic observation: hydronephrosis observed in Groups 3 and 4 but not in the control group. [24]
TAP-TA04-811:	Neonatal/ weanling and/or	Interim and Reproductive phase	Table 11: Incidence of Necropsy findings by Organ/Group Dosed from Day 21 Post-Partum- Interim phase:

[16] TAKPPI-INDNDA-00012216.
[17] "Notes on lansoprazole and dexlansoprazole nonclinical toxicity studies." at pg. 10.
[18] Pg. 105.
[19] Pg. 107.
[20] TAKPPI-SHRPNT-00710877.
[21] Pg. 8.
[22] Pg. 80.
[23] TAKPPI-CRAWFD-00007007.
[24] Pgs. 6, 11.

An Investigative Study of the Ovarian and Reproductive Effects of Lansoprazole Administered to Juvenile Female Rats[25]	juvenile female Sprague-Dawley rats		○ Dilatation pelvis: 2 female animals in group 5[26] Table 11: Incidence of Necropsy Findings by Organ/ Group Dosed from Day 21 Post-Partum- Reproductive Phase: ○ Dilatation pelvis: 1 female animal in Group 5[27]
NCTR/SV062502: Lansoprazole in the NCTR B6C3F$_1$ Neonatal Mouse Bioassay, Report NCTR/SV062502. National Center for Toxicological Research, FDA, 25 June 2002. [28]	Mouse (neonatal)	52 weeks (dosed PND 8 & 15)[29]	- I requested underlying pathology slides for this study conducted in neonatal mice dosed by intraperitoneal injection because, according to Takeda, "[t]his model was stated to be more relevant for risk assessment in children than the usual adult animal models." [30]
A-29-1488: A Two-Year Oral Oncogenicity Study of AG-1749 in Rats (One-Year Interim Report)[31]	Sprague-Dawley rat	1-year interim report from 2-year study	- I requested underlying pathology slides for this study to examine the lesions in dosed animals that are poorly defined in the report such as: Gross Pathology- Individual observations[32] - Kidney, Focus, Bilateral ○ Group 4, male- 1 mild finding: - Kidney, Focus, Unilateral, Right ○ Group 2, male-1 mild finding Gross Pathology- Individual observations[33] - Kidney, Granular surface ○ Group 5, female- 1 mild finding: Histopathology- Individual observations- Males[34]

[25] TAKPPI-INDNDA-00405717.
[26] Pg. 99.
[27] Pg. 103.
[28] TAKPPI-INDNDA-00422552.
[29] TAKPPI-MOSAIC-00081264
[30] *Id*.
[31] TAKPPI-MOSAIC-00019543
[32] Pg. 34.
[33] Pg. 35.
[34] Pg. 39.

			- Kidney, Infarct
			  o Group 4, male- 1 mild finding:
			- Kidney, Necrosis, Glomerulus, Fibrinoid
			  o Group 5, male- 1 marked finding:
			- Kidney, Nephropathy
			  o Group 1 male- 1 mild finding
			  o Group 2 male- 3 mild findings
			  o Group 3 male- 1 mild finding
			  o Group 5 male-1 mild finding; 1 marked finding
			  o Group 6 male- 1 moderate finding; 1 mild finding.
			
			Histopathology- Individual observations- Females[35]
			
			- Kidney, Calcification
			  o Group 3 female- 1 mild finding:
			- Kidney, Necrosis, Glomerulus, Fibrinoid
			  o Group 5 female- 1 moderate finding
			- Kidney, Nephropathy
			  o Group 5 female- 1 moderate finding; 1 marked finding:
			- Kidney, Nephroblastoma
			  o Group 2 female- 1 moderate finding:

A-29-439/ A-29-1388 A Twelve-Month Oral Toxicity Study in Beagle Dogs with AG-1749/ Examination of pigments observed in the renal	Beagle dog	1 year	- This study is included in Dr. Levin's notes.[37] - In A-29-439, 1 year toxicity study in Beagle dogs, "a slight increase in the incidence of brown pigment deposition in the epithelium of the renal tubules was observed."[38]

[35] Pg. 42.
[37] "Notes on lansoprazole and dexlansoprazole nonclinical toxicity studies." at pg. 10: "No changes pertaining to the kidney were detected in clinical pathology (Tables 9 and 10), organ weights (Tables 11 and 12) or histopathology (Tables 15 and 16) examinations."
[38] TAKPPI-INDNDA-01097611.

tubular epithelium in a twelve-month oral toxicity study of AG-1749 in Beagle dogs [36]			- The BGA inquired about the nature of the pigments. - 43 kidney blocks from 40 animals in A-29-439 were sent to Takeda for re-examination (A-29-1388). - After examination, Takeda concluded that the "[n]o differences in the incidence of pigment deposition in the renal tubular epithelium were observed between the control and any treated group." Takeda concluded that lipofuscin deposits caused the pigmentation.[39] - Examples of plates are provided in A-29-1388 in black-and-white.[40]
EPL Study No. 105-027: Histopathological evaluation of kidney sections from dog[41]	Beagle dog	Examination of 1 year dog study	- A pathologist reviewed the kidney pathology findings from A-29-439/ A-29-1388, and I requested this underlying report. However, this report has not been produced to me to date. "Because lipofuscin is a pigment commonly associated with membrane degradation, it was decided to review the kidney pathology using an independent pathologist (EPL Study No. 105-027). The findings from this study show that there was no evidence of an effect of treatment in the sections examined. The incidence, severity and character of the spontaneous lesions recorded were within the normal range for young laboratory beagles. The levels of lipofuscin deposition in this study are within the expected range for laboratory beagles of this age. There is no evidence to

[36] TAKPPI-INDNDA-01097607; TAKPPI-INDNDA-01097620.
[39] TAKPPI-INDNDA-01097612.
[40] *See* TAKPPI-INDNDA-01097615 copies of plates. This statement appears underneath the plates: "Note: we are not submitting originals at this time; however, we would be happy to submit them upon request."
[41] TAKPPI-MOSAIC-00019567.

			suggest low grade persistent chronic injury or any pathology of the kidney."[42]
A-29-2184 (SBL 27-91)(A-29-1731): Thirteen-Week Intravenous Toxicity Study of AG-1749 in Beagle Dogs[43]	Dog	13 weeks	- This study is included in Dr. Levin's notes.[44] Table 12, Gross pathology: - Male o Animal in the 30 mg/kg group with scar in cortex, bilateral and hemorrhage at scar and renal papilla, bilateral. None of the control animals had either finding. [45] - Female o Animal in the 30 mg/kg group with scar in cortex, unilateral. None of the control animals had this finding. [46] Table 14, Histopathology, H.E. staining: [47] - Male o Interstitial hemorrhage : Animal 25 (30 mg/kg group) o Moderate cast: Animal 25 (30 mg/kg group) o Moderate glomerular sclerosis: Animal 25 (30 mg/kg group) o Glomerular hemorrhage: Animal 25 (30 mg/kg group) o Basophilic renal tubule: Animal 25 (30 mg/kg group) o Lymphoid cell infiltration: Animal 9 (3 mg/kg group); Animals 17 & 19 (10 mg/kg group); Animal 25 (30 mg/kg group) o Moderate proliferation of connective tissue: Animal 25 (30 mg/kg group) o Moderate mineralization: Animal 25 (30 mg/kg group) o Thrombus: Animal 25 (30 mg/kg group)

[42] *Id*. at pg. 4.
[43] TAKPPI-INDNDA-01833656.
[44] "Notes on lansoprazole and dexlansoprazole nonclinical toxicity studies." at pg. 9.
[45] Pg. 82.
[46] Pg. 83.
[47] Pg. 94 (103).

			- Female:[48]
			  o Cast: Animal 30 (30 mg/kg group)
			  o Granuloma in cortex: Animal 32 (30 mg/kg group)
			  o Glomerular sclerosis: Animal 30 (30 mg/kg group)
			  o Lymphoid cell infiltration: Animal 30 (30 mg/kg group)
			  o Proliferation of connective tissue: Animal 30 (30 mg/kg group)
			
			16) Kidney[49]
			
			Chronic interstitial nephritis, i.e., glomerular sclerosis, cast, lymphoid cell infiltration and proliferation of connective tissue, was observed in one male (No. 25) and one female (No. 30) in the 30 mg/kg group. In the Azan-stained sections of the kidney, the proliferation lesion of connective tissue in the cortex was blue and fibrosis was distinct. The sections of the cortex from the two animals were Congo red and thioflavin-T negative. No findings indicating a specific pathogen (leptospire and so on) were observed in the sections with silver stain of Levaditis-method. Glomerular hemorrhage, basophilic renal tubule, interstitial hemorrhage, mineralization and thrombus were also observed in this male (No. 25). The sections of the kidney in the control group showed negative for thioflavin-T and Azan.

A-29-348 (Project No. 86-3127): A Six-Month Oral Toxicity Study in Beagle Dogs with AG-1749[50]	Beagle dog	6 months	- This study is included in Dr. Levin's notes.[51] - Examples of kidney pathology findings in dosed groups that were greater than controls: Incidence summary[52]:

[48] Pg. 100 (109).
[49] Pg. 17(26).
[50] TAKPPI-INDNDA-01097211.
[51] "Notes on lansoprazole and dexlansoprazole nonclinical toxicity studies." at pgs. 9-10.
[52] Pg. 098-104.

			- Table 15- males:
			  ○ Bilateral subacute/chronic inflammation
			  ▪ Group 1: 0 animals
			  ▪ Group 4: 1 animal
			
			- Table 16- females:
			  ○ Unilateral mineralization:
			  ▪ Group 1: 0 animals
			  ▪ Group 3: 1 animal
			  ▪ Group 4: 2 animals
			  ○ Unilateral collecting tubules dilated:
			  ▪ Group 1: 0 animals
			  ▪ Group 2: 1 animal
			  ▪ Group 3: 2 animals
			  ▪ Group 4: 2 animals
			  ○ Bilateral collecting tubules dilated:
			  ▪ Group 1: 0 animals
			  ▪ Group 2: 2 animals
			  ▪ Group 4: 1 animal
			  ○ Unilateral subacute/ chronic inflammation
			  ▪ Group 1: 0 animals
			  ▪ Group 2: 1 animal

A-29-170 (Study No. 356/SU):
 	
Thirteen-week Oral Toxicity Study of AG-1749 in Beagle Dogs [53]
	Beagle dog	13 weeks	- This study is included in Dr. Levin's notes.[54]
			
			- Histopathological findings in dosed groups not observed in controls:
			
			Table XII- Histopathology:[55]
			
			- Pigmentation of tubular epithelium:
			  ○ Group 2 male: slight finding
			  ○ Group 2 female: slight finding
			  ○ Group 3 female: slight finding
			- Hematoma in renal papilla:
			  ○ Group 2 female: slight finding
			- Fatty deposition of glomerulus:
			  ○ Group 2 female: slight finding
			- Mononuclear cell infiltration:

[53] TAKPPI-INDNDA-01282051; TAKPPI-MOSAIC-01091723.
[54] "Notes on lansoprazole and dexlansoprazole nonclinical toxicity studies" at pg. 9.
[55] TAKPPI-INDNDA-01282430.

			○ Group 2 male: slight finding ○ Group 4 male: slight finding
B-5277: Thirteen-Week Oral Gavage Toxicity Study of TAK-390 in Dogs[56]	Beagle dogs (6 months old)	13 weeks	- This study is included in Dr. Levin's notes.[57] - Histopathological findings in dosed groups not discovered in controls: Table 89- male histopathological findings (pgs. 194-195): ○ Dilatation, tubular, focal (5 mg/kg/day animal); ○ mineralization, cortical (50 mg/kg/day animal); Table 94- female histopathological findings (pg. 199): ○ Basophilia, tubular (5mg/kg day animal; 15 mg/kg/day animal; 2 lansoprazole 50 mg/kg/day animals) ○ Cast, hyaline (15 mg/kg/day animal) ○ Cell infiltration, interstitial- (2 15 mg/kg/day animals) ○ Mineralization, cortical (15 mg/kg/day animal; 2 lansoprazole 50 mg/kg/day animals)
A-29-2075 (T-33326): 13 Week Intravenous Administration Sub-Chronic Toxicity Study in the Beagle[58]	Beagle dog	13 weeks	-This study is included in Dr. Levin's notes.[59] Table III- Histopathology Incidence Table- Decedents: - Female: ○ Hyperplasia, papillary epithelium, focal; mineralization, medulla, focal in 10 mg/kg/day group[60]
A-29-1300 (Study No. 5329/su):	Beagle dog	1 week	.

[56] TAKPPI-INDNDA-00012218.
[57] "Notes on lansoprazole and dexlansoprazole nonclinical toxicity studies." at pg. 10.
[58] TAKPPI-INDNDA-01201626.
[59] "Notes on lansoprazole and dexlansoprazole nonclinical toxicity studies." at pg. 9.
[60] TAKPPI-INDNDA-01202100.

One-week Intravenous Range-Finding Study of AG-1749 in Beagle dogs[61]			Table VII Histopathology- Individual Observations including[62]
			
			- Males:
			  o Pigmentation, renal tubule:
			  ▪ Group 1 saline: 0
			  ▪ Group 2: vehicle: 0
			  ▪ Group 4: mild finding
			  o Vacuolization intracyte, renal tubule
			  ▪ Group 1 saline: 0
			  ▪ Group 2: vehicle: 0
			  ▪ Group 3: mild finding
			
			- Despite these findings, kidney histopathology findings, study authors concluded "No treatment-related abnormalities were seen in any group" [63]
			
			- I asked to review slides from this study to assess the short-term effects of lansoprazole.

A-29-806: Four-Week Intravenous Toxicity Study of AG-1749 in Beagle Dogs[64]	Beagle dog	4 weeks	- Blood chemistry: o Urea nitrogen value was increased in a female (E602) receiving 3 mg/kg/day on day 28; however, it was considered to be not treatment-related, because it showed no dose-dependency.[65] - I did not notice any renal histopathology findings noted in the report for dosed animals versus the control or vehicle groups, but I requested this study because it was a short-term IV study in the dog.
SBL 27-93: Four-Week Oral Toxicity Study of AG-1749 Enteric	Monkey	Four weeks	Histopathological findings in dosed groups not observed in controls:

[61] TAKPPI-MOSAIC-00019344.
[62] Pg. 29.
[63] Pg. 8.
[64] TAKPPI-MOSAIC-00021888.
[65] Pg. 13.

Coated Formulation in Cynomolgus Monkeys[66]			Table 17-1:[67] - Males: o Mineralization in renal papilla: 2 animals in 50 mg/kg group o Focal mononuclear cell infiltration: 1 animal in 50 mg/kg group - Females: o Focal fibrosis: 1 animal in 5 mg/kg group o Polyarteritis: 1 animal in 50 mg/kg group
A-29-467 (440/SU)(A-29-452): Thirteen Week Oral Toxicity Study of AG-1749 in Rats Followed by 4-, 13-, and 26-Week Recovery[68] & A-29-468: Thirteen-Week Oral Toxicity Study of AG-1749 in Rats followed by 26-week Recovery[69]	Wistar rat	13 weeks dosing period	- This study is included in Dr. Levin's notes.[70] - Microscopic pathology: "Dilatation of the pelvis in the right kidney was observed in 3 animals each in the control and dosed groups after the 13-week recovery period. However, from its incidence pattern, the change was not considered to be related to treatment." [71]

[66] TAKPPI-MOSAIC-00022773.
[67] *Id*. at pgs. 94 (374)- 95 (375).
[68] TAKPPI-INDNDA-01026264; TAKPPI-INDNDA-01026299-TAKPPI-INDNDA-01026300TAKPPI-INDNDA-00934441.
[69] TAKPPI-INDNDA-01026264.
[70] "Notes on lansoprazole and dexlansoprazole nonclinical toxicity studies." at pg. 6.
[71] TAKPPI-INDNDA-00934462- TAKPPI-INDNDA-00934463

EXHIBIT A

CURRICULUM VITAE

Name: Gilbert Wolfram Moeckel

Title: Professor of Pathology

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310 Cedar Street, LB20, PO Box 208023,
New Haven, CT 06520-8023
Phone: (203) 737-2803
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Cell: (203) 503-4411

Citizenship: United States of America & Germany

Education:

05/1989	MD, Ludwig-Maximillian University, Munich, Germany
06/1993	PhD, Ludwig-Maximillian University, Munich, Germany

Career/Academic Appointments:

07/93-05/96	Postdoctoral Research Fellow, Department of Medicine, Nephrology Section, University of Arizona HSC, Tucson, AZ
06/96-06/99	Resident, Department of Pathology, University of Arizona HSC, Tucson, AZ
07/99-06/00	Chief Resident, Department of Pathology, University of Arizona HSC, Tucson, AZ
07/99-06/00	Director of Resident Research, Department of Pathology, U of AZ HSC
07/00-06/08	Assistant Professor, Department of Pathology, Vanderbilt University Medical Center, Nashville, TN
07/03-06/08	Assistant Professor, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN
07/08-06/16	Associate Professor, Department of Pathology, Yale University School of Medicine, New Haven, CT
07/16-present	Professor, Department of Pathology, Yale University School of Medicine, New Haven, CT

Administrative Positions:

07/08-present	Director, Renal, Cardiac & Transplant Pathology and Electron Microscopy Laboratory, Yale University School of Medicine, New Haven, CT
07/11-present	Director, Renal Pathology and Genitourinary Pathology Fellowship, Yale University School of Medicine, New Haven, CT
04/16-06/21	Director, Pathology Faculty Mentoring Program, Department of Pathology, Yale University School of Medicine, New Haven, CT
07/08-06/21	Attending Pathologist, Autopsy Service, Yale New Haven Hospital, New Haven, CT

Medical Licenses

Connecticut #46205, Rhode Island #MD16417, Tennessee retired.

Board Certification:

Diplomat of the American Board of Pathology
(initial certification 2008, recertified 2018)

Professional Honors & Recognition

International

2011 Invited Member, Nephropathology Working Group, European Society of Pathology

2004 2nd place, Annual Essay Contest (Basic Science), Endourological Society World Congress, Mumbai, India.

National

2010 Fellow of the American Society of Nephrology, unrestricted

2000 Paul E. Strandjord Young Investigator Award, Academy of Clinical Laboratory Physicians and Scientists

1998 Travel Award, College of American Pathologists, "Concepts in Molecular Biology", American Society for Investigative Pathology, Bethesda, Maryland.

University

2018-22 Faculty Advisory Committee (FAC) to the Dean, Yale School of Medicine

2016 Master of Art (privatim), Yale University, New Haven, CT, USA

2014-15 Yale Medical Group Emerging Leaders Program, Yale School of Management, New Haven, CT

2015-2016 Yale Medical Group Advanced Emerging Leaders Program, Yale School of Management, New Haven, CT

2015 Averill A. Liebow Award for Excellence in Teaching Pathology Residents, Department of Pathology, Yale University School of Medicine

2001 Vanderbilt Physician Scientist Development Award, Vanderbilt University School of Medicine

2000 Outstanding Resident Teaching in Pathology Award, University of Arizona College of Medicine

Grant/Clinical Trials History

Active Grants

Agency: Department of Defense
Title: "MIF as Preventive Drug Against Combat Injury-Related Acute Renal Failure"

P.I. Gilbert Moeckel, MD, PhD
Percent effort: 30%
Total cost: $1,238,920
Project period: 09/01/2017-08/30/21

Agency: NIDDK/NIH/DHHS
ID# 2R01DK093771-02A1 Sub
Title: "Macrophage Function in Kidney Repair"
P.I.: Lloyd Cantley
Role in project: Co-Investigtor
Percent effort: 5%
Total cost: $225,000
Project period: 08/25/16-07/31/21

Agency: NIH/DHHS
Title: Salk Institute for Biological for Biological Studies
PI: Joe Craft
Project period**:** 03/01/18-01/31/22
Title: *Mitochondrial DNA Stress Activation of Interferon Signaling and Lupus Pathology*
Major Goal: We endeavor to address the role of mtDNA in lupus pathology in mice and humans.
Role: Co-Investigator 5%

Current Clinical Trials
NA

Past Grants

Agency: Univ. of Southern California
Title: **"**Building a Kidney Partnership Project Program"
P.I.: Lloyd Cantley
Role in project: Co-Investigtor
Percent effort: 5%
Project period: 02/01/17-01/31/19

Agency: MIFCOR, Inc.
Title: *Pharmacokinetics of MIF-2/D-DT Therapy in Renal I/R Injury*
P.I. Moeckel
Percent effort: 10%
Project period: 02/06/18-01/31/19

Agency: NIH/NIDDK
I.D.# R43 DK092005
Title: "The synthesis of novel selective LPA1 receptor antagonists for evaluation in animal models of renal fibrosis"
P.I. Anil Karihaloo, PhD

Role on Project: Co-Investigator
Percent effort: 2%
Direct cost per year: $74,951
Total cost per project period: $124,311
Project period: 03/01/14-02/28/17

Agency: Boehringer Ingelheim
Title: "Molecular Markers of Diabetic Nephropathy Progression in Humans"
P.I. Gilbert Moeckel, MD, PhD
Percent effort: 15%
Total cost per project period: $950,451
Project period: 01/07/13-01/30/16

Agency: Alexion Pharmaceuticals
I.D.# HIC#1007007166
Title: "Eculizumab Therapy for Chronic Complement-Mediated Injury in Kidney Transplantation: A Randomized, Open-labeled, Pilot Intervention Trial"
P.I.: Sanjay Kulkarni, MD
Role on Project: Co-investigator
Percent effort: 2%
Direct cost per year: $331,000
Total cost for project period: $994,107
Project period: 07/01/11-06/30/16

Agency: NIH/NIDDK
I.D.# RO1DK093770
Title: Novel Kidney Injury Tools in Deceased Organ Donation to Predict Graft Outcome
P.I.: Chirac Parikh
Role on Project: Co-Investigator
Percent effort: 2%
Direct cost per year: $462,521
Total cost per project period: $1,425,500
Project period: 08/15/13-06/30/16

Agency: NIH/NIDDK
I.D.# 5P30DK090744-02
Title: Center for Polycystic Disease Research at Yale
P.I.: Michael Caplan, MD, PhD
Role on Project: Co-Investigator, (Core A: Animal Models Core)
Percent effort: 5%
Direct cost per year: $ 682,503
Total cost for project period: $5,532,955
Project period: 09/30/10-06/30/15

Agency: NIH/NIDDK
I.D.# RO3 DK077700-02

Title: "Role of COX2 in Medullary Interstitial Cell Survival and Function"
P.I. Gilbert Moeckel MD, PhD
Percent effort: 75%
Total cost per project period: $150,000
Project period: 04/01/07-03/30/11

Agency: NIH/NIDDK
I.D.# 1RO1 DK069921
Title: "The Role of MT-MMPs in Renal Development";
P.I. Roy Zent, MD, PhD
Role on Project: Co-Investigator
Percent effort: 5%
Total cost per project period: $1,000,000
Project period: 04/01/05-03/31/10

Agency: NIH/NIDDK
I.D.# 1RO1 DK071090
Title: "Molecular Genetics and Pathogenesis of ARPKD",
P.I. Guanging Wu, MD
Role on Project: Co-Investigator
Percent effort: 5%
Total cost per project period: $1,000,000
Project period: 10/01/05-09/30/10

Agency: NIH/NIDDK
I.D.# 1R01 DK62373
Title: "Genetic Mechanisms of Polycystic Kidney Disease";
P.I. Guanging Wu, MD
Role on Project: Co-Investigator
Percent effort: 5%
Total cost per project period: $ 1,000,000
Project period: 05/01/03-02/28/08

Agency: NIH/NIDDK
I.D.# K08 DK059975
Title: "Role of Organic Osmolytes in Renal Papillary Necrosis"
P.I. Gilbert Moeckel, MD, PhD
Percent effort: 75%
Total cost per project period: $596,430
Project period: 07/01/03-06/30/08

Agency: NIH/NIDDK
I.D.# O'Brien Center for Excellence in Nephrology Pilot Grant
Title: "Role of Interstitial Cell Survival in Medullary Blood Flow Regulation"
P.I. Gilbert Moeckel MD, PhD
Percent effort: 75%

Total cost per project period: $ 40,000
Project period: 07/01/2006-06/30/2008

Agency: NIH/NIDDK
I.D.# R21 DK064743
Title: "Genetic Analysis of C.elegans Cellular Osmoregulation."
P.I. Kevin Strange, PhD
Role on Project: Co-Investigator
Percent effort: 5%
Total cost per period: $ 150,000
Project period: 07/01/02-06/30/05

Agency: Vanderbilt University
I.D. Physician Scientist Development Program Award
Title: "Role of Organic Osmolytes in Renal Medullary Cell Survival"
P.I. Gilbert Moeckel, MD, PhD
Percent effort: 75%
Total cost per project period: $200,000
Project period: 07/01/01-06/30/03

Pending Grants

NA

Invited Speaking Engagements, Presentations, Symposia & Workshops

International

2020 Invited Speaker, Clinical Diabetes Forum, Department of Medicine, Osaka University, ABENO HARUKAS Conference Center, Osaka, Japan, July 15, 2020, "Acute Injury To The Kidney Proximal Tubule And How To Repair It",

2019 IZKF Visiting Professor, University Erlangen, Germany, December 16, 2019 "MIF-2/D-DT is a cytokine with cell protective and regenerative function in the kidney proximal tubule".

2019 Invited Speaker, ISN World Congress of Nephrology, Melbourne, Australia, April 12-15, 2019, "Diagnostic Criteria of Tubular Injury in Kidney Biopsies".

2018: Invited Speaker, 9th International MIF Conference, Ludwig Maximillians University, Munich, Germany, October 3-6, 2018, "Role of D-DT in Autophagy Regulation".

2016: American Society of Nephrology (ASN), Renal Week, Clinical Nephrology Conference, Renal Biopsy: Clinical Correlations, Chicago, IL, Nov 15-20

2016: Invited Lecturer, "Biopsy Diagnosis of Acute Interstitial Nephritis" sponsored by Chinese National Further Education Project, First Affiliated Hospital of Wenzhou Medical University, June 20-26, 2016

2015: Invited Lecturer, 7th International MIF Symposium, Weizmann Institute of Science, Rehovot, Israel, October 25-28, 2015, "Role of MIF in Renal Tubular Epithelial Cell Regeneration".

2014: XXXth Congress of the International Academy of Pathology 2014, Bangkok, Thailand, October 5-10, 2014, Renal Pathology Session: "Granulomatous Interstitial Nephritis".

2008: American Society of Nephrology (ASN), Renal Week, Clinical Nephrology Conference, Renal Biopsy: Clinical Correlations, Philadelphia, PA.

2007: FLEET Inc. Advisory Panel Meeting, Atlanta, GA, "Protective effect of Citrate on renal phosphate crystal formation in male and female Sprague-Dawley rats".

2007: Moderator and Speaker, Scientific Session "Stress and Transport", American Society of Nephrology, Renal Week, San Francisco, CA, October 31- November 5, 2007

2006: United States and Canadian Academy of Pathology (USCAP), Annual Meeting, Renal Pathology Evening Specialty Conference, Atlanta, GA. "Lupus Vasculitis"

2006: Hamburg University, Eppendorf Clinic, Nephrology Division, Hamburg, GER, "Hypertonicity-induced Apoptosis and Signaling in Medullary Interstitial Cells".

2005: Gordon Conference: Cellular Osmoregulation: Sensors, Transducers and Regulators; Salve Regina University, Newport, RI, "Role of COX2 in Medullary Cell Survival".

2004 ASN Renal Week, Basic Science Symposium, St. Louis. MO, "Anti-Apoptotic Properties of Osmolytes".

2004: International Polyol Pathway Conference, Kona, HI, "Organic Osmolytes Prevent Hypertonic Stress-Induced Apoptosis In Renal Medullary Interstitial Cells".

National

2021 Invited Speaker, Pathology Grand Rounds, Department of Pathology, Boston University, Boston, MA, April 28, 2021

2018 Invited Lecturer, Benjamin Sturgill Lectureship, Department of Pathology and Division of Nephrology, University of Virginia, Charlottesville, VA, December 11, 2018

2016: Board Review Course, American Society of Nephrology (ASN), The Transplant Kidney Biopsy: Indications and Correlations, Chicago, IL, August 4, 2016

2016: Pathology Grand Rounds, Department of Pathology and Laboratory Medicine, University of Wisconsin-Madison, "Role of MIF/CD74-dependent Signaling in Tubular Epithelial Cell Regeneration".

2016: Pathology seminar, Department of Pathology and Laboratory Medicine, Brown University, Providence, RI, "A Potpourri of Renal Biopsy Cases"

2016: Nephrology Research Talk, Section of Nephrology, Northwestern University, Chicago, "Role of MIF in Acute Kidney Injury".

2015: Invited Lecturer, 8th Annual Yale Fibrosis Symposium, Yale West Campus Conference Center, Yale University, New Haven, April 23-24, 2015, "Renal Fibrosis".

2015: Rheumatology Grand Rounds, Department of Medicine, Rheumatology Section, Yale University School of Medicine, "Lupus Nephritis".

2015: Research Seminar, Department of Medicine, Nephrology Section, Yale University School of Medicine, "Role of Kidney Medullary Progenitor Cells in Tubular Epithelial Cell Repair".

2014: Research Seminar, Department of Pathology, Louisiana State University Health-Shreveport, "Renal Medullary Interstitial Cells are Pericytes With a Role in Cell Injury Repair".

2013: Pathology Grand Rounds, Department of Pathology, Yale University School of Medicine, "Killing You Softly: Progression of Fibrosis in CKD".

2008: Pediatric Nephrology Research Conference, Pediatric Nephrology Division, Vanderbilt University Medical Center, "Hyperosmotic Stress-induced Signaling and Survival Mechanisms in Renal Medullary Interstitial Cells".

2006: University of Arizona, Department of Medicine, Nephrology Division, Tucson, AZ, "Prostanoid-dependent Survival Mechanisms in Renal Medullary Interstitial Cells".

2006: University of Maryland, Department of Medicine, Nephrology Division, Baltimore, MD, "Hypertonicity-induced Apoptosis and Signaling in Medullary Interstitial Cells".

2006: Renal Research Conference, Nephrology Division, Vanderbilt University Medical Center: "Cell Volume-dependent Signaling Activates COX2 and NFAT5 in a Macula Densa Cell Line".

2006: NIDDK Young Investigator Meeting, Adelphi, MD. "Organic Osmolytes Prevent Activation of Hypertonicity-induced Mitochondrial Pro-Apoptotic Pathways."

2004 Grand Rounds, Department of Pathology, Indiana University, Indianapolis, "Role of COX2 in Renal Cell Survival & Death".
2000 Department of Pathology, East Virginia College of Medicine, Norfolk, VA,"Role of Organic Osmolytes in Renal Papillary Cell Survival."

Peer-Reviewed Presentations & Symposia Given at Meetings Not Affiliated With Yale

International

2017 ASN Renal Week, New Orleans, LA, "Role of MIF-2 in proximal tubular cell proliferation and survival" Akinobu Ochi and Gilbert Moeckel.
2016 ASN Renal Week, Chicago, IL, "Hyperglycemia-dependent Epigenetic and Gene Expression Profiles in Human Kidney Mesangial Cells". Akinobu Ochi and Gilbert Moeckel.
2016 USCAP Annual Meeting, Seattle, WA, "Characterizing the Inflammatory Infiltrate in Human Kidney Biopsies with TIN". Grace Chuang and Gilbert W. Moeckel.
2015 ASN Renal Week, San Diego, CA, "Kidney Tumors: What is important for Nephrologists?" Gilbert W. Moeckel.
2014 ASN Renal Week, Pennsylvania, PA, "Kidney Medullary Progenitor Cells in Tubular Epithelial Cell Repair". Gilbert W. Moeckel and Dong Chen.
2012 ASN Renal Week, San Diego, CA, "Kidney Stem Cell Responses in Acute Kidney Injury Repair", Gilbert W. Moeckel and Dong Chen.
2011 ASN Renal Week, Philadelphia, PA, "The Spectrin-based Cytoskeleton Organizes Differential functional Domains Along The Mouse Nephron", Michael Stankewich, Gilbert W. Moeckel, Thomas Ardito, Lan Ji and Jon S. Morrow.
2009 ASN Renal Week, San Diego, CA, "Effect of Acute Phosphate Exposure on Kidney Function". Zhonghai Chen, PhD, Dong Chen, MD and Gilbert Moeckel, MD, PhD.
2008 ASN Renal Week, Philadelphia, PA "Resolution of Renal Inflammation: A new Role for NF-kappa B1 (p50) in Inflammatory Kidney Diseases" Ulf Panzer, Oliver Steinmetz, Udo Helmchen, Gilbert Moeckel, Gunter Wolf, Rolf AK Stahl, Friedrich Thaiss.
2008 ASN Renal Week, Philadelphia, PA " Thromboxane Receptor Deletion Ameliorates Adriamycin-Induced Glomerular Injury in Mice with Podocyte COX2 overexpression" Huifang Cheng, Youfei Guan, Thomas M. Coffman, Gilbert W. Moeckel, Raymond C. Harris.
2007 ASN Renal Week, San Francisco, CA, "Effect of Citrate on Calcium Phosphate Crystal Formation in Male and Female Sprague-Dawley Rats". Li Zhang and Gilbert W. Moeckel
2006 ASN Renal Week, San Diego, CA, "Effect of Dietary Phosphate and Dehydration on Calcium Phosphate Crystal Formation in Sprague Dawley Rats Following Ischemia Reperfusion Injury". Li Zhang, Victor Ruiz, Gilbert Moeckel.
2006 ASN Renal Week, Molecular Regulation of Osmolytes and Organic Solute Transporters, San Diego, CA, "Tyrosine Kinase Signaling to TonEBP/NFAT5 in Medullary Interstitial Cells."
2005 ASN Renal Week, Cell and Transport Physiology, Philadelphia, PA, "ERK phosphorylation stimulates COX2 and TonEBP expression in MMDD1 cells".

2005 ASN Renal Week, Philadelphia, PA. C4d Staining and Donor Specific Antibodies inRenal Allograft: Diagnostic and Therapeutic Implications. Heidi Schaefer, Gilbert Moeckel, Agnes Fogo, Harold Helderman et al.

2005 ASN Renal Week Philadelphia, PA. The Role of COX2 Expression in Self Limited Podocyte Injury. Huifang Cheng, Gilbert W. Moeckel, Ray Harris et al.

2005 USCAP Annual Meeting, Feb 26 –March 4, 2005 San Antonio, Tx. "COX2-dependent Osmolyte Accumulation and Gene Expression in Medullary Interstitial Cells". Li Zhang and Gilbert W. Moeckel, Vanderbilt University Medical Center, Nashville, TN.

2005 ASN Renal Week Philadelphia, PA. " ERK phosphorylation stimulates COX2 and TonEBP expression in MMDD1 cells". Li Zhang, Raymond Harris, Victor Ruiz and Gilbert W. Moeckel.

2005 ASN Renal Week, Philadelphia, PA. A Mouse Pkhd1 Mutant Model Produced by Gene-Targeting Exhibits a Phenotypic Complex of Human ARPKD. Lichun Wang, Gilbert W. Moeckel, Guanqing Wu et al.

2005 ASN Renal Week, Philadelphia, PA. Integrin alpha-1 beta-1 is a Negative Regulator of Glomerulosclerosis in Diabetic Mice. Ambra Pozzi, Gilbert W. Moeckel, Matthew D. Breyer et al.

2005 ASN Renal Week, Philadelphia, PA. Podocyte Expression of Beta 1 Integrin is Necessary to Maintain Glomerular Filtration Barrier Integrity. Roy Zent, Gilbert W. Moeckel and Ambra Pozzi et al.

2004 ASN 37th Annual Meeting, St. Louis, MO. ERK ½ Phosphorylation Mediates Osmolyte Accumulation in Mouse Medullary Interstitial Cells. Li Zhang and Gilbert W. Moeckel.

2004 ASN 37th Annual Meeting, St. Louis, MO. Characterization of mice with the targeted mutation in Pkhd1Sae-youll Cho[1,2], Hong Wang[1,2], Gilbert Moeckel[3], Huaqi Xiong [1,2], Dan Liang[1,2], Sujin Park[1,2], InGyu Kim[1,2], Tianbing Ding[1,2], Guanqing Wu[1,2]. [1]Dept. of Medicine, [2]Dept. of Cell & Devel. Biol. [3]Dept. of Pathology, Vanderbilt University, TN 37232.

2004 ASN 37th Annual Meeting, St. Louis, MO. Adriamycin induces podocyte injury in nephrin-COX-2 transgenic mice. Huifang Cheng, M.D* 1, Suwan Wang 1, Chuanming Hao, M.D* 1, Gilbert W Moeckel, M.D* 1, Mingzhi Zhang, M.D 1, Yan Zhao 1, Arunima Datta 1, Chris Kennedy, PhD* 2, Matthew D Breyer, M.D* 1 and Raymond C Harris, M.D* 1. 1 Medicine, Vanderbilt University, Nashville, TN, United States and 2 Nephrology, University of Ottawa, Ottawa, Ontario, Canada .

2004 USCAP Annual Meeting, Vancouver, BC. Heterogenous Signaling of Hypertonic Stress-Induced Osmolyte Response in Kidney Cells. L Zhang and G. W. Moeckel.

2003 ASN 36th Annual Meeting, San Diego. PKHD1, a Gene Product Related to Autosomal Recessive Polycystic Kidney Disease (ARPKD), Is Developmentally Regulated. W. Mai, M. Chang, G.W. Moeckel, R. Zhao. et al.

2003 ASN 36th Annual Meeting, San Diego. The pck Rat, a Mutant Model of Autosomal Recessive Polycystic Kidney Disease (ARPKD), Shows Reduced Expression of PKHD1 in the Cystic Epithelia of the Kidney. J. Wang, W. Mei, G.W. Moeckel, M. Zhang, R. Zhao, et al.

2003 ASN 36th Annual Meeting, San Diego. Betaine Decreases Hyperosmotic Stress-induced Cytochrome c Release in Medullary Interstitial Cells. L. Zhang, C.M. Hao, M.D. Breyer and G.W. Meckel.

2003 ASN 36th Annual Meeting, San Diego. COX2-dependent Osmolyte Accumulation in Macula Densa Cells. G.W. Moeckel, L. Zhang, H.F. Cheng and R.C. Harris.

2003 FASEB Meeting, San Diego, CA, Genetic and Physiological Characterization of Cellular Osmoregulation in the Nematode C. elegans. S.T. Lamitina, K.Baman, R. Morrison, G. Moeckel and K. Strange.

2003 ASN, Renal Week Oral Presentation, San Diego, CA,"COX2-Dependent Osmolyte Accumulation in Macula Densa Cells".

2002 USCAP Annual Meeting, Chicago, IL. Role of Integrin Alpha 1 in Glomerulosclerosis. Gilbert W. Moeckel, S. Chang, X. Chen, S. Shankland, R. Zent and A. Pozzi.

2002 ASN 35th Annual Meeting, Philadelphia, PA. Role of Integrin □1□1 in Regulation of Renal Medullary Osmolyte Concentrations in Mice under Diuresis and Antidiuresis. Gilbert W. Moeckel, Li Zhang, Roy Zent, Ambra Pozzi.

2002 ASN 35th Annual Meeting, Philadelphia, PA. COX2-Inhibition Decreases Organic Osmolyte Accumulation in Renal Medullary Cells In Vitro and In Vivo. Gilbert W. Moeckel, Li Zhang, Chuan-Ming Hao, Agnes B. Fogo and Matthew D Breyer.

National

2005 American Urology Association (AUA) Annual Meeting, San Antonio, TX. "A simple method for achieving renal parenchymal hypothermia for pure laparoscopic partial nephrectomy". S. Duke Herrell III, Gilbert W. Moeckel and Todd M. Webster.

2002 AUA Annual Meeting, Orlando, FL. Osmolyte Profile of Renal Cell Carcinoma and Primary Culture Supernatants: HPLC Quantification and Oligomicroarray Analysis.Louis Liou, Provash Sadhukan, Joseph DiDonato, Andrew Novick and Gilbert Moeckel.

2000 Annual Meeting of the Academy of Clinical Laboratory Physicians and Scientists, Salt Lake City, UT. Effect of Organic Osmolytes on Membrane ATPases and Osmotic Fragility in Red Blood Cells. Gilbert W. Moeckel, Ramin Shadman and Sayed M.H. Sadrzadeh.

2000 Annual Meeting of the AACC, San Francisco, CA. Inhibition of Erythrocyte Membrane ATPase Activity by Organic Osmolytes Betaine, Sorbitol, and Inositol. Gilbert W. Moeckel, Ramin Shadman and Sayed M.H. Sadrzadeh

Professional Service

Peer Review Groups/Grant Study Section:
2007- present Ad hoc reviewer, National Science Foundation

2005-2008 Reviewer, American Heart Association, Southern Affiliate Grant Applications

Advisory Boards

2015-present Member, Regional Advisory Committee on aHUS, Alexion Inc.

2005-2009 Member, Advisory Committee on OSPS-induced Renal Injury, FLEET Inc.

Journal Service

Member of Editorial Board

2013-2019 American Journal of Physiology, Cell Physiology
2011-present International Scholarly Research Network (ISRN), Practice in Nephrology
2012-2016 Universal Journal of Clinical Medicine, General Medicine
2006-present Reviewer for PNAS, Journal of Cell Physiology, Journal of American Society of Nephrology, Nephrology Dialysis & Transplantation, American Journal of Physiology, Kidney International, Annals of Internal Medicine.

Professional Service for Professional Organizations:

American Society of Investigative Pathology (ASIP)

2019-present Member, Research and Science Policy Committee

American Society of Nephrology (ASN)

2015-present Lecturer, ASN Board Review Course & Update.

2012-2013 Member, Program Committee for Renal Week 2013

Reviewer

2017 & 2015 Abstract reviewer, Renal Week 2015, Abstract Submissions to Basic/Experimental Pathology
2007 Abstract reviewer, Renal Week 2007, Abstract Submissions to Cell and Transport Physiology
2005 Abstract reviewer, Renal Week 2005, Abstract Submissions to Renal Pathology

United States and Canadian Academy of Pathology (USCAP)

2012-2015 Member, Abstract Review Board, Electron Microscopy

Renal Pathology Society (RPS)

2016-2019 Member, Finance Committee
2014-2016 Member, Program Committee
2013-2015 Member, Nomination and Awards Committee
2011-2013 Chair, Research Committee
2010-2011 Member, Nomination and Awards Committee
2009-2010 Member, Membership Committee
2007-2008 Member, Research Committee

Yale University Service:

2014-2017 Member of Yale University IRB HIC Committee IV.
2017-2022 Member of Faculty Advisory Committee (FAC) to the YSM Dean.
2019-2022 Mentoring Committee, Faculty Advisory Committee to Dean Brown

Department Committees

2020-present Faculty Compensation Advisory Committee, Department of Pathology, Yale School of Medicine.
2020-present Award Nomination Committee, Department of Pathology, Yale School of Medicine.
2020-present Immunology Advisory Committee, Department of Pathology, Yale School of Medicine.
2016-2021 Director, Faculty Mentoring Program, Department of Pathology, Yale School of Medicine.
2015-2021 Member, Fellowship Clinical Competency Committee, Department of Pathology, Yale School of Medicine.
2014-2016 Residency Clinical Competency Committee, Department of Pathology, Yale School of Medicine.
2013-2015 Member, Resident Education Committee, Department of Pathology, Yale School of Medicine.
2009-2015 Member, Outreach Committee, Department of Pathology, Yale School of Medicine.

Public Service:

Mentoring College & High School Students:

2020-2022 **Benjamin Wu**, Horace Mann School, Bronx, NY, USA: "Digital Pathology and Application of Machine Learning to Diagnosis in Lung, Kidney and Liver Tissues", manuscript in preparation.
2019-2022 **Xue Li**, MD, postdoctoral fellow, Yale University, CT: Project:" The role of Medullary Interstitial Cells in Proximal Tubule Cell survival".
2019-2022 **Shruti Chinchanikar**, MD, postdoctoral fellow, Yale University, CT: Project:" The role of DDT-dependent Akt signaling in cell survival".
2019-2020 **Johannes Eisenberg**, University of Connecticut, Storrs, CT: Project: "D-DT-dependent cell survival signaling mechanisms."
2018-2020 **August Fridell**, University of North Carolina, Chapel Hill, NC: Project: "Role of Medullary Interstitial Cell in Acute Tubular Injury Repair"

2015-2017 **Nickolas Moeckel**, Guilford High School, Guilford, CT, Project: "Role of DDT in Proximal Tubule Injury and Repair".

2012-2014 **David Shan**, Choate Rosemary Hall, Wallingford, CT, Project: "Identification and Characterization of a Novel Phosphate Receptor in Vascular Smooth Muscle Cells". Semifinalist, Siemens Competition in Math, Science & Technology 2014.

2011-2012 **Chang Park**, Hopkins School, New Haven, CT, Project: "Aldosterone-dependent Fibronectin Synthesis in Kidney Fibroblasts". Semifinalist, Intel Science Talent Search 2011.

2010-2012 **Yuning Zhang**, Guilford High School, Guilford, CT, Project: "Isolation & Characterization of Stem Cells from the Kidney Medulla". Semifinalist, Siemens Competition in Math, Science & Technology 2011. Semifinalist, Intel Science Talent Search 2011.

Bibliography:

Peer-Reviewed Original Research

1. **Gilbert W. Moeckel**, Hans Günther Dasser, Tian Jun Chen, Michael Schmolke and Walter G. Guder. Bicarbonate dependent betaine synthesis in rat kidney. In: Renal Ammonia genesis and Interorgan Cooperation in Acid-Base Homeostasis. Tizianello A, ed. Contribution to Nephrology, Basel, Karger, 1994, vol 110, pp 46-53.
2. **Gilbert W. Moeckel**, Jürgen Hallbach and Walter G. Guder. Purification of human and rat kidney aldose reductase. Enzyme Protein 1994, 48:45-50.
3. **Gilbert W. Moeckel** and Yeong Hau H. Lien. Bicarbonate dependency of betaine synthesis in cultured LLC-PKI cells. American Journal of Physiology 1994, 266:F512-F515.
4. **GW Moeckel**. Studien zur Entwicklung eines distal tubularen diagnostischen Markers aus der menschlichen Niere. Deutsche Gesellschaft fuer Klinische Chemie Mitteilungen 25 Heft 2, 1994, p. 47-49.
5. **Gilbert W. Moeckel**, Li-Wen Lai, Walter G. Guder, H. Moo Kwon and Yeong-Hau H. Lien. Kinetics and osmoregulation of Na- and Cl-dependent betaine transporter in rat renal medulla. American Journal of Physiology 1997, 272(Renal Physiol. 41):F100-F106.
6. **Gilbert W. Moeckel** and Yeong-Hau H. Lien. Distribution of de novo synthesized betaine in rat kidney: role of renal synthesis on medullary betaine accumulation. American Journal of Physiology 1997, 272(Renal Physiol. 41):F94-F99.
7. L-W Lai, **GW Moeckel** and Y-HH Lien. Kidney-targeted liposome-mediated gene transfer in mice. Gene Therapy 1997, 4:426-431.
8. Stefan Pummer, William H. Danzler, Yeong-Hau H. Lien, **Gilbert W. Moeckel**, Katharina Völker and Stefan Silbernagl. Reabsorption of betaine in Henle's loops of rat kidney in vivo. American Journal of Physiology 2000, 278:F434-F439.
9. Xiong H, Chen Y, Yi Y, Tsuchiya K, **Moeckel G,** Cheung J, Liang D, Tham K, Xu X, Chen XZ, Pei Y, Zhao ZJ, Wu G. A novel gene encoding a TIG multiple

domain protein is a positional candidate for autosomal recessive polycystic kidney disease. Genomics Jul; 2002, 80(1):96-104.

10. Hui-Fang Cheng, Connie J. Wang, **Gilbert W. Moeckel**, Ming-Zhi Zhang, James A. McKanna and Raymond C. Harris. A selective cyclooxygenase-2 inhibitor retards progressive renal injury in a model of diabetes and hypertension. Kid Int 2002, 62(3):929-939.
11. **Gilbert W. Moeckel**, Ramin Shadman, Joy M. Fogel and Sayed M.H. Sadrzadeh. Organic osmolytes betaine, sorbitol and inositol are potent inhibitors of erythrocyte membrane ATPases. Life Sciences 2002, 71(20):2413-2424.
12. **Gilbert W. Moeckel**, Li Zhang, Chuan-Ming Hao, Agnes B. Fogo, Ambra Pozzi and Matthew D. Breyer. COX2 activity promotes organic osmolyte accumulation adaptation of renal medullary interstitial cells from hypertonic stress. J Biol Chem 2003, 278(21):19352-19357.
13. Z.Wang, J.K. Chen, S. Wang, **G. Moeckel** and C. Harris. Importance of functional EGF receptors in recovery from acute nephrotoxic injury. J Am Soc Nephrol 2003, 14: 3147-3154.
14. S.T. Lamitina, K. Baman, R. Morrison, **G. W. Moeckel** and K. Strange. Adaptation of the nematode C. elegans to extreme osmotic stress. Am J Physiol, Cell Physiol, 2004:286:C785-91.
15. Naohiko Koshikawa, Susann Schenk, **Gilbert W. Moeckel**, Andrew Sharabi, Kaoru Miyazaki, Humphrey Gardner, Roy Zent and Vito Quaranta. Proteolytic processing of laminin-5 by MT1-MMP in tissues and its effects on epithelial cell morphology. FASEB J, 2004:18:364-6.
16. M.Z. Zhang, W. Mai, C. Li, C. Hao, **G. Moeckel**, G. Wu et al. PKHD1 protein encoded by the gene for autosomal recessive polycystic kidney disease associates with basal bodies and primary cilia in renal epithelial cells. Proc. Natl. Acad. Sci. USA 2004 Feb 24:101:2311-6.
17. X. Chen, **G. Moeckel**, D. Cosgrove, J. Morrow, R. Harris, A.B. Fogo, R. Zent and A. Pozzi. Lack of Integrin {alpha}1{beta}1 Leads to Severe Glomerulosclerosis after Glomerular Injury. Am J Pathol, 2004 Aug;165(2):617-630.
18. Lee W, Glaeser H, Smith LH, Roberts RL, **Moeckel GW**, Gervasini G, Leake BF, Kim RB Polymorphisms in human organic anion transporting polypeptide 1A2: Implications for altered drug deposition and CNS drug entry. J Biol Chem 2005 Mar 11;280(10):9610-7.
19. Cheng H, Zhang M, **Moeckel GW**, Zhao Y, Wang S, Qi Z, Breyer MD, Harris RC. Expression of mediators of renal injury in the remnant kidney of ROP mice is attenuated by cyclooxygenase-2 inhibition. Nephron Exp Nephrol 2005, Jun 30;101 (3):e75-e85
20. **GW Moeckel**, L Zhang, X Chen, M Rossini, R Zent and A Pozzi. Role of integrin α1ß1 in the regulation of renal medullary osmolyte concentration. Am J Physiol,2006, 290:F223-31.
21. Zent, Roy; Su, Yan; Hudson, Billy G; Borza, Dorin-Bogdan; **Moeckel, Gilbert**; Qi, Zhonghua; Breyer, Matthew; Voziyan, Paul; Pozzi, Ambra. "Glomerular injury is exacerbated in diabetic integrin Beta1-null mice" Kidney International 2006, Aug;70(3):460-70.

22. Cheng H, Wang S, Jo Yi, Hao CM, Zhang M, Fan X, Kennedy C, Breyer MD, **Moeckel GW**, Harris RC. Overexpression of Cyclooxygenase-2 Predisposes to Podocyte Injury. J Am Soc Nephrol. 2007 Feb;18(2):551-9.
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Chapters, Books and Reviews

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Case Reports

1. **Gilbert W. Moeckel**, Kathy Jabs and Agnes B. Fogo. An 11-year-old African American girl with systemic lupus erythematosus and ANCA-negative renal vasculitis. Am J Kid Dis 2002, 39(2):433-438.
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EXHIBIT B

Materials Considered by Expert Dr. Gilbert W. Moeckel
All materials referenced and/or discussed within general opinion report are incorporated herein by reference.
Depositions:
David Crawford - March 1, 2018 - full transcript and exhibits
Stuart Levin - February 21, 2019 - full transcript and exhibits
Labels:
Dexilant Product Labels 2009-2020 found at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022287
Prevacid Product Labels 1995-2020 found at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020406
Designated Confidential Documents Produced by Takeda:
TAKPPI-CRAWFD-00005323
TAKPPI-CRAWFD-00005819
TAKPPI-GIRARA-00031378
TAKPPI-INDNDA-00140996
TAKPPI-INDNDA-00188307
TAKPPI-INDNDA-00283167
TAKPPI-INDNDA-01035045
TAKPPI-KARPEO-00023702
TAKPPI-KNIPFN-00004316
TAKPPI-KNIPFN-00269785
TAKPPI-LEVINS-00001908
TAKPPI-LEVINS-00002489
TAKPPI-LEVINS-00002502
TAKPPI-LEVINS-00002567
TAKPPI-LEVINS-00002598
TAKPPI-MOSAIC-00019567
TAKPPI-MOSAIC-00020775
TAKPPI-MOSAIC-00941511
TAKPPI-MOSAIC-01147625

TAKPPI-MOSAIC-01306116
TAKPPI-NORDMC-00014668
TAKPPI-NORDMC-00015010
TAKPPI-PREVPM-00009999
TAKPPI-PREVPM-00010280
TAKPPI-ROGERR-00057582
TAKPPI-SHRPNT-00849558
TAKPPI-SHRPNT-01079357
Takeda Conducted Non-Clinical and Clinical Trials of Prevacid and Dexilant:
14-091/SU: TAKPPI-SHRPNT-00710877
17-006/tk: TAKPPI-CRAWFD-00007007
6764-342; TAP-TB04-801: TAKPPI-PREVPM-00008406; TAKPPI-MOSAIC-00021851; Renal Histopathology Slides
85-2992; A-29-174; AG-1749-13009: TAKPPI-MOSAIC-00022451
86-3108; A-29-438: TAKPPI-MOSAIC-00022783; TAKPPI-MOSAIC-00935791; Renal Histopathology Slides
A-29-03989; 05-186/CO; AB15BP.2G3P.BTL: TAKPPI-INDNDA-00392111; Renal Histopathology Slides
A-29-04092; 06-226/CO; AB15BP.2G3P.03.BTL: TAKPPI-MOSAIC-00022011; Renal Histopathology Slides
A-29-04147: TAKPPI-MOSAIC-00022012
A-29-1300: TAKPPI-MOSAIC-00019344
A-29-1388: TAKPPI-INDNDA-01097607

A-29-1488: TAKPPI-MOSAIC-00019543
A-29-167: TAKPPI-INDNDA-01282051
A-29-168: TAKPPI-INDNDA-01282051
A-29-169: TAKPPI-INDNDA-01097032
A-29-170; 356/SU: TAKPPI-INDNDA-01282051; TAKPPI-MOSAIC-01091723
A-29-1863: TAKPPI-INDNDA-01629899; TAKPPI-INDNDA-01629900; TAKPPI-INDNDA-01630391; TAKPPI-INDNDA-01630392; TAKPPI-INDNDA-01081077; TAKPPI-INDNDA-01080582
A-29-1979; TA90-152; R&D/90/339; R&D/93/547; Study 126-052; TD91-025: TAKPPI-INDNDA-01105845; TAKPPI-MOSAIC-01307709; TAKPPI-MOSAIC-01308862; TAKPPI-SHRPNT-00716294; TAKPPI-MOSAIC-01082828; TAKPPI-MOSAIC-01264493; TAKPPI-MOSAIC-01264495; TAKPPI-MOSAIC-01264503; TAKPPI-MOSAIC-01285518; TAKPPI-MOSAIC-01341317; TAKPPI-MOSAIC-01082844; TAKPPI-MOSAIC-01341297; TAKPPI-MOSAIC-00977288; TAKPPI-MOSAIC-01061470; TAKPPI-MOSAIC-01338720; Renal Histopathology Slides
A-29-1984; TA90-152; R&D/90/339: TAKPPI-INDNDA-01045257; TAKPPI-INDNDA-01045753; Renal Histopathology Slides
A-29-1986; 126-057; TD91-276; R&D/93/731: TAKPPI-INDNDA-01620126; TAKPPI-INDNDA-01620609; TAKPPI-INDNDA-01621004; TAKPPI-INDNDA-01621366; TAKPPI-INDNDA-01621367; TAKPPI-INDNDA-01621368; Renal Histopathology Slides
A-29-2075; 586/36-1050; T-33326: TAKPPI-INDNDA-01201626
A-29-2116; TAP-01-105512-1.0: TAKPPI-MOSAIC-00020775
A-29-2142; Study 94026: TAKPPI-INDNDA-01201307

A-29-221: TAKPPI-INDNDA-01550261
A-29-345: TAKPPI-MOSAIC-01111145; TAKPPI-INDNDA-01104648; TAKPPI-INDNDA-01104879
A-29-348; 86-3127: TAKPPI-INDNDA-01097211
A-29-439; A-29-1388; 86-3109; AG-1749-12883: TAKPPI-INDNDA-01097607; TAKPPI-INDNDA-01097951; TAKPPI-INDNDA-01097952
A-29-452; 440-SU: TAKPPI-INDNDA-00934441
A-29-467; 440/SU: TAKPPI-INDNDA-01026264
A-29-468; 550/SU: TAKPPI-INDNDA-01026264
A-29-504: TAKPPI-INDNDA-01714927
A-29-505; 830-su: TAKPPI-INDNDA-01833652
A-29-680; 87-3158: TAKPPI-INDNDA-01098350; TAKPPI-MOSAIC-01082802; TAKPPI-MOSAIC-01003581; TAKPPI-MOSAIC-01209253; TAKPPI-MOSAIC-00976248; TAKPPI-MOSAIC-00976250; TAKPPI-MOSAIC-00976252; TAKPPI-MOSAIC-00976254; TAKPPI-MOSAIC-00976256; TAKPPI-MOSAIC-00976258; TAKPPI-MOSAIC-01003583; TAKPPI-MOSAIC-01307708; TAKPPI-MOSAIC-01448045; TAKPPI-MOSAIC-01209258; TAKPPI-MOSAIC-01448043; Renal Histopathology Slides
A-29-681; 1148/CA; 86-3028: TAKPPI-INDNDA-01600508; GSK-PRV-00001106; Renal Histopathology Slides
A-29-707; 279/su: TAKPPI-MOSAIC-00021671
A-29-723; 956-SU: TAKPPI-INDNDA-01626318

A-29-765; 5530-su: TAKPPI-INDNDA-01714927
A-29-767; 5338-su: TAKPPI-INDNDA-01833660
A-29-805; 985/SU: TAKPPI-MOSAIC-00019360
A-29-806: TAKPPI-MOSAIC-00021888
AG-1749-15367: TAKPPI-INDNDA-00201527
B-5277: TAKPPI-INDNDA-00012218
NCTR/SV062502: TAKPPI-INDNDA-00422552
SBL 27-91; A-29-1731; A-29-2184; A-29-1861: TAKPPI-INDNDA-01676827; TAKPPI-INDNDA-01833656
SBL 27-93; A-29-1911: TAKPPI-INDNDA-01097952; TAKPPI-MOSAIC-00022773
TA91-024; A-29-1977; R&D/93/546: TAKPPI-INDNDA-01078825; TAKPPI-MOSAIC-00022435; Renal Histopathology Slides
TAK390/00006; 00-367/SU: TAKPPI-PREVPM-00065659
TAK-390MR/00175; B-5278: TAKPPI-INDNDA-00012216
TAP TB00-814; Study 774-010: TAKPPI-INDNDA-00479099; Renal Histopathology Slides
TAP-TA03-805; Study 900285; TAP-07-006514-1.0: TAKPPI-SHRPNT-00711230; Renal Histopathology Slides

TAP-TA-04-811: TAKPPI-INDNDA-00405717
TAP-TA97-832; TAP-01-105547-1.0; TAP-03-002047-1.0; TAP-03-002048-1.0; 774-008: TAKPPI-INDNDA-00188093; TAKPPI-INDNDA-00188094; TAKPPI-INDNDA-00188095; TAKPPI-INDNDA-00188096; Renal Histopathology Slides
TD90-019; R&D/91/164: TAKPPI-INDNDA-01045753; Renal Histopathology Slides
TD90-027; PPRD/90/094: TAKPPI-MOSAIC-00021914
TD90-382; R&D/90/380: TAKPPI-INDNDA-01833657
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11-5-2010: FDA Gastrointestinal Drugs Advisory Committee Meeting Transcript
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10-27-2014: FDA Citizen Petition Response regarding Seeking Boxed Warning and Other Safety Labeling Changes for PPI Products - OSE RCM# 2011-2606; Docket# FDA-2011-P-0741; signed by Peter Diak, David Shih, Robert Levin, Scott Proestel, and Gerald Dalpan
10-29-2014: FDA Pharmacovigilance Memorandum regarding Acute Interstitial Nephritis; NDA 22-287 - signed by Carolyn Volpe and Peter Diak
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Dr. Gilbert Moeckel General Expert Opinion Report (and attachments thereto) dated April 22, 2021

EXHIBIT C

Fee Schedule

My hourly fee for expert services is $400/hour.

My hourly fee for deposition and trial testimony is $500/hour.

Testimony over the last four years

1. Diana Dominguez vs. Raghu Juvvadi, M.D.; and Access Healthcare Physicians, L.L.C.(January 15, 2020 – Circuit Court of the 5th Judicial Circuit, Hernando County, FL)
2. Patricia McGilliard vs. Kaye Zuckerman, M.D., et al. (January 29, 2020 – Superior Court of New Haven)